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PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $10.00

Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago.
Under the Act of Congress of March 3, 1879

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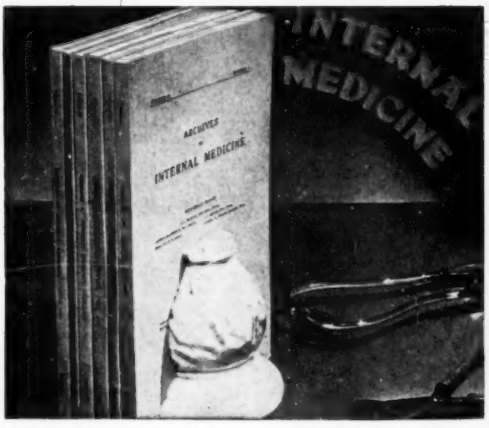

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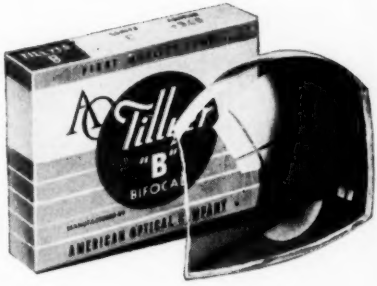

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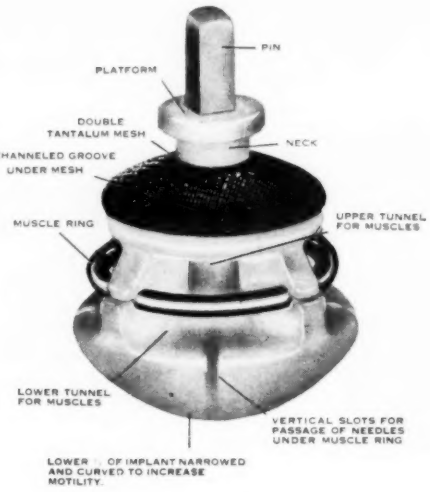

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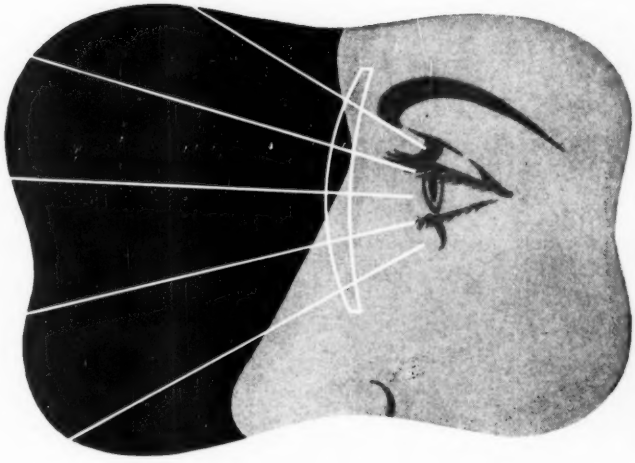

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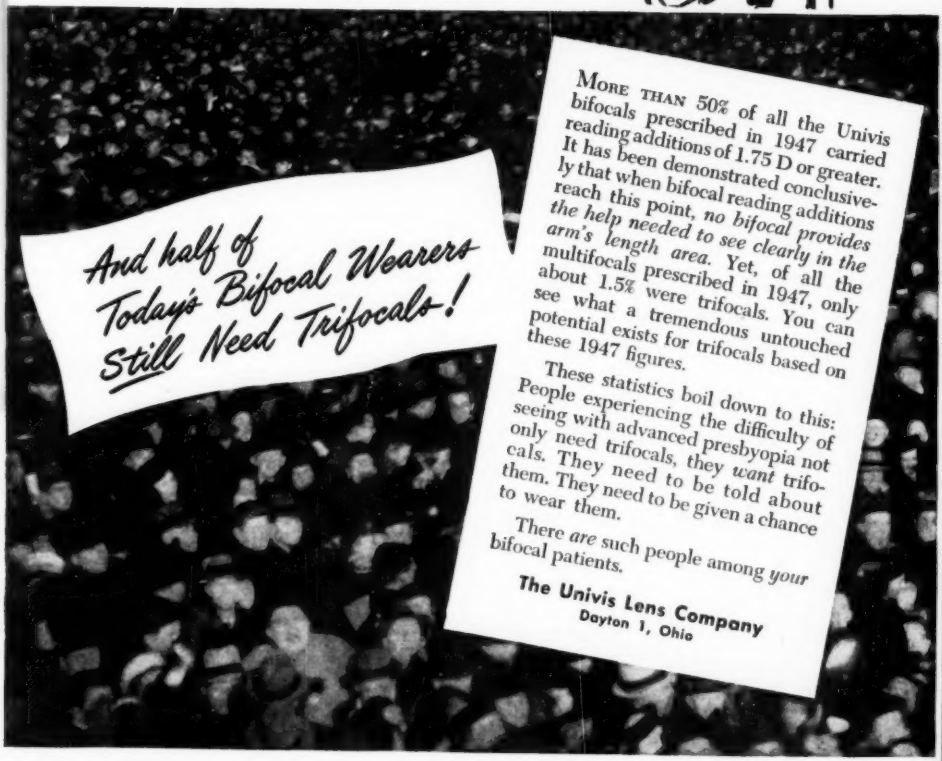

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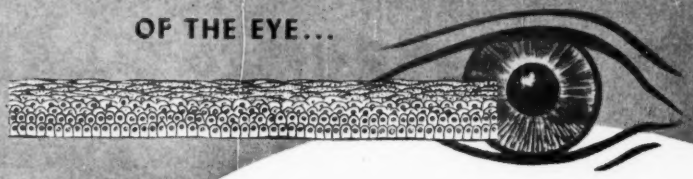

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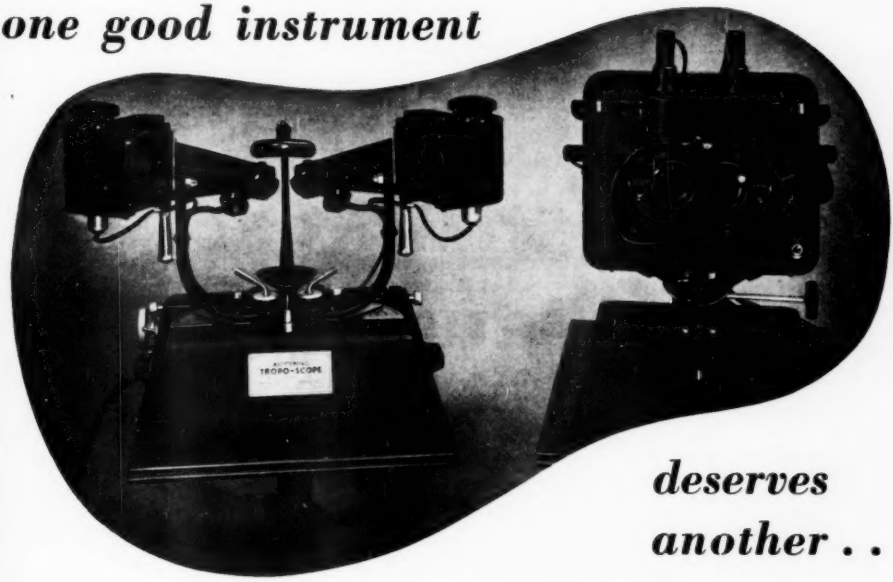

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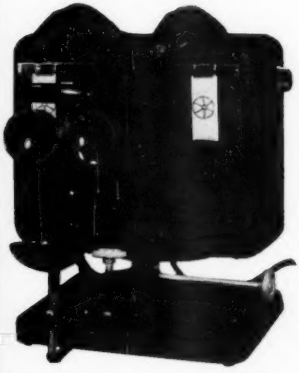

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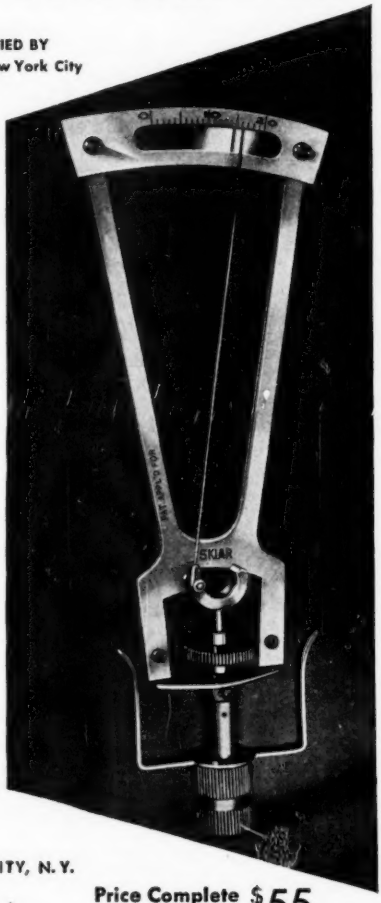

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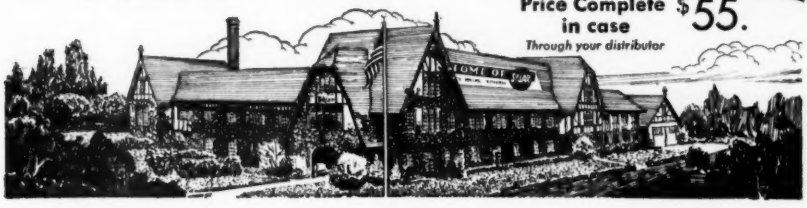

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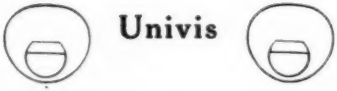

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ROLE OF INHERITANCE IN GLAUCOMA

ADOLPH POSNER, M.D.
AND
ABRAHAM SCHLOSSMAN, M.D.
NEW YORK

HEREDITY is often stressed as an important factor in the pathogenesis of glaucoma. Yet, to date, only approximately 90 pedigrees of families with glaucoma have been reported in the literature. Since these family trees are presented as isolated examples, without relation to glaucoma as a whole, they create the impression that hereditary glaucoma is rare and that it is different from the nonhereditary form.

In the course of a study of 373 cases of primary glaucoma, we were impressed by the high incidence of patients displaying familial tendencies. Fifty-one patients had one or more relatives affected with the disease. As early as 1880, Schenkl [1] stated that there is hardly an ophthalmologist who has not met with several hereditary cases. In fact, many patients demonstrate their awareness of the hereditary possibilities of the disease by the questions they put to the ophthalmologist. There is obviously a discrepancy between the paucity of the material in the literature and the everyday experience of the physician. A new approach is needed to the study of the role of inheritance in glaucoma, especially in the light of the more recent advances in genetics. While this paper represents a limited experience, it is hoped that the pooling of similar studies will supply enough data for a more adequate investigation of this genetic problem.

Correlations made in the preparation of this survey suggested the possibility of using the hereditary group as a starting point for the investigation of some of the more elusive problems in glaucoma, such as (1) the preglaucomatous state, (2) the possibility of predicting the probable severity of the disease and (3) the relation between glaucoma and certain constitutional diseases.

Recently, emphasis has been placed on the early recognition of glaucoma. Lowenstein and Schoenberg [2] studied the apparently unaffected

Presented in part at the Fifty-Second Annual Meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 15, 1947.

1. Schenkl: On the Heredity of Glaucoma, Prag. med. Wchnschr. **5**:413-414, 1880.

2. Lowenstein, O., and Schoenberg, M. J.: Pupillary Reactions of the Seemingly Unaffected Eye in Clinically Unilateral Simple Glaucoma, Arch. Ophth. **31**:392-398 (May) 1944.

eye in cases of monocular glaucoma by means of pupillography and found that the pupillary reactions were similar in the two eyes. Bloomfield and Lambert [3] used the lability test as an aid to early diagnosis. Downey [4] emphasized the importance of differences in tension between the two eyes as indicating a tendency toward glaucoma. Moreu [5] attempted to investigate the preglaucomatous state by correlating the various clinical findings.

The term "preglaucoma" was introduced by Gradle [6] in 1924. As used by him, however, it refers to glaucoma in a mild or early stage. It should be emphasized that "preglaucoma" must be differentiated from the preclinical stage, in which the eye is clinically normal. In order to gain insight into the preclinical stage, one is obliged to study normal persons.

Since the incidence of glaucoma in the general population is at most 0.5 to 2 per cent, it is obviously impossible to subject a random sample of normal persons to any series of clinical tests in the hope of shedding light on the preclinical stage. It would seem more advisable to use the families of patients with glaucoma. Schoenberg [7] reported on the results of the use of the Knapp epinephrine test in the brothers, sisters and children of patients with glaucoma. The hereditary group is particularly suited to such a study because it represents a sample with a high incidence of glaucoma and because of the mathematical probability that some members who are normal at present will ultimately have the disease.

To the patient and to his family, it is of the utmost importance to know whether his disease will follow a mild course or will lead to blindness. In fact, too little emphasis has been placed on this vital question, which is discussed elsewhere in greater detail.[8] The genetic approach is helpful in predicting the probable course in a case of glaucoma.

In taking careful pedigrees in routine cases of glaucoma, we have noted a high incidence of certain metabolic and regulatory diseases, such as diabetes, hypertensive vascular disease and obesity, among the unaffected members of the family. It is possible that there exists

3. Bloomfield, S., and Lambert, R. K.: The Lability of Ocular Tension, Arch. Ophth. **34**:83-94 (Aug.) 1945.

4. Downey, H. R.: Unequal Tension as a Sign in Early Glaucoma, Tr. Am. Ophth. Soc. **43**:495-504, 1945.

5. Moreu, A.: El problema del glaucoma verum, Buenos Aires, Salvat Editores, 1946, pp. 103-139.

6. Gradle, H. S.: Preglaucoma, Am. J. Ophth. **29**:520-523, 1946

7. Schoenberg, M. J.: The Knapp Adrenalin Mydriasis Reaction in Direct Descendants of Patients with Primary Glaucoma, Tr. Am. Ophth. Soc. **22**:53-59, 1924.

8. Posner, A., and Schlossman, A.: Mild Glaucoma, Am. J. Ophth. **31**:679 (June) 1948.

a genetic relation among all these diseases.[9] This problem is a difficult one; and, in view of the fact that we became aware of these possibilities while the present study was in progress, it was impossible to collect sufficient data to permit us to arrive at any definite conclusions.

REVIEW OF LITERATURE

Since the cases reported in the literature are not representative of the total experience with glaucoma, no definite information is available as to the relative incidence of cases showing familial tendencies. Only Biró[10] has attempted to estimate the incidence of hereditary cases among the patients with glaucoma in his clinic. Of 761 patients, 43 had a familial history of the disease. They belonged to 36 families and comprised 5.6 per cent of the total series.

Benedict,[11] in 1842, was, so far as we know, the first to call attention to the familial tendencies of the disease. He reported glaucoma in two dark-eyed daughters of an extremely gouty old general. Arlt[12] sketchily described 3 families in 1860, and Bowman[13] added another family tree in 1865. The latter referred to glaucoma as the "most subtle of the hereditary affections of the eye." In 1869, however, von Graefe,[14] while he did not report any pedigrees, stated that he had seen many cases with familial tendencies. He discussed certain observations regarding the nature of hereditary glaucoma. He stated that in many cases there were long prodromal periods, ranging from eight to sixteen years. In 1 case a mother and daughter were stricken with glaucoma in the same year, although there was an age difference of 26 years between the two. This and other cases led him to formulate the concept of anticipation, or the tendency for the disease to appear at an earlier age in succeeding generations. He also reported that noncongestive glaucoma was far less frequent among the hereditary cases than was inflammatory glaucoma. Glees and Ried,[15] on the other hand, stated that the chronic simple form is more commonly familial.

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9. Lowenstein, O.: Personal communication to the authors.

10. Biró, I.: Primary Glaucoma: Notes on the Heredity of Glaucoma, Ophthalmologica **98**:43-50, 1939.

11. Benedict, T. W. G.: Abhandlungen aus dem Gebiete der Augenheilkunde, Breslau, 1842, pp. 123-132.

12. von Arlt, C. G.: Die Krankheiten des Auges für praktische Artzte, Prague, F. A. Credner, 1860, vol. 2, pp. 190-209.

13. Bowman, W.: Ophthalmic Miscellanies, Ophth. Hosp. Rep., London **5**:1-15, 1866.

14. von Graefe, A.: Pathology and Treatment of Glaucoma, Ophth. Hosp. Rep., London **7**:112, 1871-1873.

15. Glees, M., and Ried, A.: Glaucoma in a Pedigree of Three Gener... Arch. f. Ophth. **142**:495-502, 1940.

The pedigrees in the literature fall into three main groups: (1) those in which all the affected members have juvenile glaucoma; (2) those in which, owing to anticipation, the parents or grandparents have adult glaucoma, while in the succeeding generations the affected members have juvenile glaucoma; (3) those in which all the affected members have adult glaucoma.

The first two groups include some of the most carefully worked-out pedigrees. Plocher [16] and Berg [17] traced glaucoma in six generations. Harlan,[18] Courtney and Hill,[19] Stokes [20] and Glees and Ried [15] reported pedigrees in which the disease was present in five generations. Several excellent family trees tracing glaucoma in young people through several generations were presented by Allmares,[21] Preobrazhenskiy,[22] Zorab,[23] Neamé,[24] Calhoun,[25] Howe,[26] Werner,[27] Kaufman,[28] Snell,[29] Biró [10] Allen and Ackerman [30] and Shumway.[31]

In the third group there are few pedigrees which have been followed for even three generations. This is due partly to the difficulty in following hereditary disease later in life and partly to the fact that some patients with potential glaucoma do not live long enough to reach the age at which they would have the disease. From the relative preponderance of the reported pedigrees which are concerned with

16. Plocher, R.: Contribution to Juvenile Familial Glaucoma, Klin. Monatsbl. f. Augenh. **60**:592-620, 1918.

17. Berg, F.: Glaucoma in Young Persons, Acta ophth. **10**:568-587, 1932.

18. Harlan, H.: A Case of Hereditary Glaucoma, J. A. M. A. **5**:285-286 (Sept. 12) 1885.

19. Courtney, R. H., and Hill, E.: Hereditary Juvenile Glaucoma Simplex, Tr. Sect. Ophth., A. M. A., 1931, pp. 47-68.

20. Stokes, W. H.: Primary Glaucoma: Pedigree with Five Generations, Arch. Ophth. **24**:885-909 (Nov.) 1940.

21. Allmares, F.: Familial Glaucoma in Two Generations, Ztschr. f. Augenh. **95**:276-279, 1938.

22. Preobrazhenskiy, V. V.: Hereditary Glaucoma in Young Persons, Vestnik oftal. **16**:326-332, 1940.

23. Zorab, A.: Glaucoma Simplex Familiaris, Tr. Ophth. Soc. U. Kingdom **52**:446-460, 1932.

24. Neamé, H., in discussion on Zorab.[23]

25. Calhoun, F. P.: Hereditary Glaucoma Simplex, J. A. M. A. **63**:209-215 (July 18) 1914.

26. Howe, L.: A Family History of Blindness from Glaucoma, Arch. Ophth. **16**:72-76, 1887.

27. Werner, S.: Hereditary Juvenile Glaucoma: Four Cases, Acta ophth. **7**:162-168, 1929.

28. Kaufmann, F.: Statistics on the Heredity of Eye Diseases, Wchnschr. f. Therap. u. Hyg. des Auges **9**:68-69, 1928.

29. Snell, A. C.: Hereditary Glaucoma Simplex (Juvenile Glaucoma), New York State J. Med. **23**:151-154, 1923.

30. Allen, T. D., and Ackerman, W. G.: Hereditary Glaucoma in a Pedigree of Three Generations, Arch. Ophth. **27**:139-156 (Jan.) 1942.

31. Shumway, in discussion of Courtney and Hill.[19]

juvenile glaucoma one forms the erroneous impression that juvenile glaucoma is the most commonly inherited form. In our experience, adult hereditary glaucoma is by far the commoner type. This is what one might expect, in view of the relative infrequency of juvenile glaucoma in general. Of the cases described in this paper, 5 belong to the juvenile and 45 to the adult type; none of our pedigrees show inheritance limited to the juvenile form.

Lawford [32] has treated the subject of inheritance of adult glaucoma more extensively than any other author. He described 5 family trees in which glaucoma came on after 40 years of age. All these patients had chronic simple glaucoma except 2, who had the acute congestive type.

Kirkpatrick [33] described a Jewish family in which 4 members, belonging to three generations, acquired glaucoma after the age of 40. Briggs [34] and James [35] published pedigrees which showed insidious onset of glaucoma in adults over 40. Other pedigrees have been described by Schenkl,[1] Jacobson,[36] Nettleship,[37] Rogman,[38] Usher,[39] Pagenstecher [40] and Holland.[41] Bartels [42] described "glaucoma climactericum" in a mother and 4 daughters.

The question arises whether there is any real difference between juvenile and adult glaucoma. This is extremely important for the study of heredity, for, if there were no essential difference, we should be able to pool certain pedigrees without regard to the age of onset.

32. Lawford, J. B.: Examples of Hereditary Glaucoma, Roy. London Ophth. Hosp. Rep. **17**:57-64, 1907-1908; Examples of Hereditary Glaucoma, ibid. **19**:42-44, 1913-1914.

33. Kirkpatrick, cited by Bell, J., in Pearson, K.: Anomalies and Diseases of the Eye, pt. 5, Treasury of Human Inheritance, Eugenics Laboratory Memoirs XXVII, London, Cambridge University Press, 1926, vol. 2, p. 514.

34. Briggs, A. H.: Familial Primary Glaucoma in Adults, Brit. J. Ophth. **23**:649-59, 1939.

35. James, R. R.: Pedigree of a Family Showing Hereditary Glaucoma, Brit. J. Ophth. **2**:438-443, 1937.

36. Jacobson, J.: Contributions to the Study of Glaucoma, Arch. f. Ophth. **32**:96-168, 1886.

37. Nettleship, E.: Some Hereditary Diseases of the Eye, Ophthalmoscope **4**:549, 1906.

38. Rogman, A.: On the Pathogenesis of Chronic Glaucoma: A Glaucomatous Family, Ann. ocul. **5**:73-75, 1899.

39. Usher, C. H., cited by Bell, J., in Pearson, K.: Anomalies and Diseases of the Eye, pt. 5, Treasury of Human Inheritance, Eugenics Laboratory Memoirs XXVII, London, Cambridge University Press, 1926, vol. 2, p. 524.

40. Pagenstecher, H. A.: Klinische Beobachtungen aus der Augenheilanstalt zu Wiesbaden, Wiesbaden, C. W. Kiredel, 1861.

41. Holland, H. I.: Hereditary Glaucoma Affecting Three Generations, Indian M. Gaz. **59**:408, 1924.

42. Bartels, V.: Chronic Hereditary Climacteric Glaucoma, Ztschr. f. Augenh. **48**:298, 1922.

Most authors accept 35 years as the upper age limit for the onset of juvenile glaucoma. It is obvious that when an arbitrary age limit is set many cases must fall into this group for no other reason than that the disease is discovered before the patient has attained the age limit. Glaucoma may exist without symptoms for several years and thus may not be detected until a few years after its incipience. Moreover, chronologic age is not a sound criterion to follow in dealing with biologic processes. There is a fundamental weakness in the use of an arbitrary age limit in defining a disease, especially since the characteristics of the disease are not essentially different in the two age groups and since authorities differ as to the age limit.

Anderson [43] stated the belief that hydrophthalmos is the result of a structural defect early in life, while senile glaucoma is due to degenerative factors associated with the aging process. He placed juvenile glaucoma somewhere between these two types, and he assumed that both factors are pathogenetic in this intermediate group. Supporting this thesis from a hereditary point of view are 4 pedigrees reported by Löhlein,[44] Berg,[17] Strehler [45] and Korte,[46] respectively. In these pedigrees, hydrophthalmos occurred in the same family in which other members had juvenile or adult glaucoma. Franceschetti,[47] on the other hand, claimed that hydrophthalmos is transmitted as a recessive character.

According to Anderson,[48] 87 per cent of cases of hydrophthalmos are recognized before the end of the first year of life, while Löhlein's [44] figures show that 78.9 per cent of juvenile glaucoma appears between the ages of 15 and 30, with a peak of 38.8 per cent between the ages of 16 and 20. Haag,[49] on the other hand, showed a gradually increasing percentage of patients with glaucoma, starting with 0.4 per cent at the age of 1 to 10 years and rising to 31.9 per cent in the age group of 61 to 70 years. Of his cases of juvenile glaucoma, 61.2 per cent began at 26 to 35 years of age. This is in line with our own statistics on juvenile glaucoma. These figures lead to the conclusion that hydrophthalmos is purely congenital, while juvenile and adult glaucoma are distinct from hydrophthalmos and may be regarded as the same disease. It is possible that in a small proportion of cases juvenile glaucoma may be related to hydrophthalmos.

43. Anderson, J. R.: Hydrophthalmia or Congenital Glaucoma, London, Cambridge University Press, 1939, p. 8.

44. Löhlein, W.: Juvenile Glaucoma, Arch. f. Ophth. **85**:393-488, 1913.

45. Strehler, cited by Korte.[46]

46. Korte, W.: Contribution to the Heredity of Glaucoma, Klin. Monatsbl. f. Augenh. **102**:664-668, 1939.

47. Franceschetti, A., in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 1, pp. 713-714.

48. Anderson,[43] pp. 5-16.

49. Haag, C.: Juvenile Glaucoma, Klin. Monatsbl. f. Augenh. **54**:133-167, 1915.

The incidence of cases of hereditary glaucoma in the age groups below 35 years has been estimated to be 18 (Keerl [50]) and 20 per cent (Löhlein [44]) of all cases of glaucoma.

One argument which is frequently offered to prove that juvenile glaucoma is distinct from adult glaucoma is the preponderance of myopia in the younger group. Löhlein gave the incidence of myopia in cases of juvenile glaucoma as 50 per cent. In Plocher's pedigree, which is often cited as corroborating evidence, there were 17 cases of myopia. In most of these cases the degree of myopia was —1.00 D. or less and in only 4 was the myopia over 3 D. Our series of patients with glaucoma of all ages shows an incidence of 18 per cent myopia.[51] It is possible to account for some of the cases of myopia in the juvenile group by assuming that the increased tension results in a stretching of the young eye. An alternative view was held by von Graefe,[14] who stated the belief that myopia and glaucoma show similar mechanisms of inheritance. Our statistics do not show a greater incidence of myopia among the cases of juvenile glaucoma than in the over-all series. We have 5 cases of myopia above —0.5 D. among 23 patients whose glaucoma began earlier than 35 years of age.

Since there is no fundamental difference between juvenile and adult glaucoma in the signs, symptoms and course of the disease, we may group them together in our study of heredity.

Glaucoma is said to be more prevalent among persons of certain races. Jews and Negroes are thought to be more susceptible. Hereditary glaucoma has been reported from all parts of the world. Dérer [52] described a pedigree in Czechoslovakia. Ibrahim [53] published 2 pedigrees from Egypt, and Holland [41] reported 2 from India. Rampoldi [54] and Cassini [55] described several cases in Italy. Preobrazhenskiy [22] and Makarov [56] reported pedigrees from Russia. Waardenburg [57] described

50. Keerl, M.: Juvenile Glaucoma, Inaug. Dissert., Leipzig, Emil Lehmann, 1920.

51. Posner, A., and Schlossman, A.: The Clinical Course of Glaucoma: A Review of 474 Cases from Private Practice, Am. J. Ophth. **31**:915 (Aug.) 1948.

52. Dérer, J.: Juvenile Glaucoma, Bratisl. lekár. listy **10**:600-602, 1930.

53. Ibrahim, F. G.: Two Glaucomatous Families, Bull. Ophth. Soc. Egypt **34**:28-30, 1941.

54. Rampoldi, R.: Due note voli osservazioni di glaucoma, Ann. di ottal. **13**: 347-351, 1884.

55. Cassini, F.: Simple Chronic Glaucoma in Eight Members of Family, Arch. ottal. **47**:1-15, 1940.

56. Makarov, N. Y.: Peculiar Hereditary Form of Idiopathic Glaucoma in Transbaikal, Vestnik oftal. **10**:850-855, 1937.

57. Waardenburg, P. J.: Das menschliche Auge und seine Erbanlagen, The Hague, M. Nijhoff, 1932, pp. 327-343; Observations on the Heredity in Borderline Cases Between Juvenile and Senile Glaucoma, Also Between Infantile and Juvenile Glaucoma, Arch. f. Ophth. **140**:662-686, 1939.

a family tree in Netherlands. Examples are available in the American, French,[58] Scandinavian and German literatures.

Various hypotheses have been advanced to account for the inheritance of the disease. Bowman [13] suggested that an inherited disposition of the vessels or nerves might be supposed to be the primary seat of the disease. Priestley Smith [59] published a small pedigree in which father and daughter had abnormally small eyeballs. Elliot [60] expressed the same idea. Nettleship [37] suggested that there might be an inherited disproportion of the cornea, ciliary body and lens, or the inheritance of weakness in the lamina cribrosa. The combination of hereditary glaucoma and myopia has been discussed.

Mousselevitch [61] implicated the endocrine glands. He described a woman in whom glaucoma developed in the right eye two weeks after the first confinement and in the left eye after the second confinement. Her mother also became blind after childbirth. Her brother and grandfather were afflicted with glaucoma. Franceschetti [47] expressed the belief that only the tendency to glaucoma is inherited.

PRESENTATION OF PEDIGREES

Fifty-one patients, belonging to 30 different families, have come under our observation. Some were patients of the late Dr. Mark J. Schoenberg. Forty-eight additional persons with known glaucoma have been found in this group but have not been examined by us.

The patients have been classified into four groups according to type, namely, acute congestive glaucoma, chronic congestive glaucoma, chronic simple glaucoma with congestive attacks and chronic simple glaucoma. This classification follows that of Schmidt-Rimpler,[62] who recognized the existence of a congestive phase in certain cases of chronic simple glaucoma. The reasons for the use of this nomenclature are given elsewhere.[51] Pupillographic examinations were carried out by Dr. Otto Lowenstein on 6 glaucomatous patients and 14 normal relatives. For all the patients and for 3 of the relatives the findings were similar to those found in cases of primary glaucoma.[63] In addition to the customary

58. Le Quang, R.: Hereditary Glaucoma, Paris, Ed. Jel, 1935.

59. Smith, P.: An Instance of Hereditary Glaucoma and Its Cause, Ophth. Rev. **13**:215-226, 1894.

60. Elliot, R. H.: A Treatise on Glaucoma, London, Oxford University Press, 1922, pp. 134-136.

61. Mousselevitch, cited by Preobrazhenskiy.[22]

62. Schmidt-Rimpler, H.: Glaukom und Ophthalmomalacia, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, Leipzig, W. Engelmann, 1908, vol. 6, pt. 1.

63. Lowenstein, O., and Schoenberg, M. J.: Nervous Factor in the Origin of Simple Glaucoma, Arch. Ophth. **31**:384-391 (May) 1944.

provocative tests, some of the patients were subjected to the Knapp epinephrine test [64] and to the jugular compression test of Schoenberg.[65]

FAMILY 1.—Both the father and the mother had glaucoma. The mother refused surgical treatment and became blind at the age of 65. Of their 6 children, 3 have glaucoma. All but Sam have chronic simple glaucoma. Sam has chronic simple glaucoma with congestive attacks, which began after the institution of miotic therapy. Louis was followed for fourteen years. The grandchildren are not old enough to permit one to form any conclusions on the basis of this pedigree.

FAMILY 2.—Bertha has chronic simple glaucoma which began with an acute congestive attack in both eyes following use of atropine for refraction. Her case demonstrates that even juvenile glaucoma may take a benign course. Her aunt (Anna) has chronic simple glaucoma. Bertha's visual fields continued to contract, although the tension had been reduced to 11 and 18 mm. Her sister; who also has dementia precox, had an acute congestive attack shortly after confinement in a psychiatric institution. According to the history, Bertha's mother had glaucoma. Constitutional diseases, such as hypertensive vascular disease, toxic goiter and disease of the coronary arteries are prevalent in this family. Bertha was observed for thirteen years and her aunt for twenty-one years.

FAMILY 3.—Esther and her father, Jacob, both have chronic simple glaucoma. The former has emmetropia and the latter high hypermetropia. In both, the disease pursues a moderately severe course. Jacob was kept under observation for twenty-one years. The onset of glaucoma in Esther's left eye was at the age of 34, while the disease developed in the right eye at the age of 36. This case illustrates the futility of attempting to draw a sharp line of distinction between adult and juvenile glaucoma by using the age of 35 as the dividing line. Families 2 and 3 show anticipation.

FAMILY 4.—Two sisters have chronic simple glaucoma of a mild form. Several other members of the family have the disease. Both sisters are asymptomatic, and their disease was discovered because of the history of glaucoma in the family. Neither showed increase of tension after use of homatropine. Carrie's left eye, however, showed a positive reaction to the jugular compression test. The glaucoma in her right eye began sixteen years after the onset in the left eye. Carrie was followed for twenty-five years and Rosa for fifteen years. These cases show how mild a course chronic simple glaucoma may pursue in certain cases.

FAMILY 5.—Two sisters have mild glaucoma. In 1 of them, Babette, the disease is of the chronic simple type, while in the other, Gisella, acute glaucoma developed after use of atropine but responded well to miotics. The third sister, Ethel, had two acute attacks in the same eye. Ethel was observed for thirteen years and Gisella for fourteen years. At the age of 60 their father had onset of chronic simple glaucoma, which necessitated surgical intervention, but he retained his vision up to the time of his death, at the age of 80. One sister and 2 children of another sister have convergent strabismus. The entire family displays a strong tendency to psychoneurosis.

FAMILY 6.—All 3 sisters have acute congestive glaucoma. The ages of onset were 17, 39 and 71 years, respectively. Their mother first had glaucoma at the age of 60. Thus, 2 sisters show anticipation, while the third one does not. Of

64. Knapp, A.: The Action of Adrenalin on the Glaucomatous Eye, Arch. Ophth. **50**:550-559 (Nov.) 1927.

65. Schoenberg, M. J.: Experimental Study of Intraocular Pressure and Ocular Drainage, J. A. M. A. **61**:1098-1103 (Sept. 27) 1913.

5 eyes with glaucoma in this sibship, 3, belonging to 3 different members, had to be enucleated because of poor response to iridectomy. One eye showed a good result after cyclodialysis. One of the sisters (Rose) maintained a tension of between 35 and 40 mm. of mercury for over twenty years without loss of field.

FAMILY 7.—The disease in father (Abraham) and daughter (Shoshana) began as asymptomatic chronic simple glaucoma. The father had monocular glaucoma. Four months after treatment with pilocarpine was instituted, he began to have congestive attacks. He was observed for thirteen years. The daughter had an acute attack in the right eye one day after cyclodialysis of the left eye. She was followed for ten years. All 3 affected eyes reacted poorly to operation on the iris. The daughter's right eye behaved relatively well for seven years after cyclodialysis. Cases of this type, which begin as chronic simple glaucoma, respond poorly to miotics, lose the fields rapidly and go on to blindness after surgical measures involving trauma to the iris, are, fortunately, infrequent. In the hereditary group there was 1 other such case (family 27), and 8 additional cases occurred among the remaining 323 cases of glaucoma in our series.

FAMILY 8.—Lottie has mild glaucoma, while her brother, John, has a severe form of the disease. A presumptive diagnosis of glaucoma was made for Lottie's condition twenty-five years ago. She suffers from recurrent blurring and ocular discomfort. On several occasions the tension was found to be elevated. Pupillographic examination showed a curve similar to that found for primary glaucoma. She has been under observation for eighteen years, has retained normal vision in each eye and has not lost any of the visual field. The brother, on the other hand, has become blind in one eye and has retained only a central island of vision of 5 degrees in the other. He has been observed for seventeen years. Their father had onset of glaucoma at the age of 67, but none of his nine brothers and sisters had the disease. A case such as Lottie's shows the importance of differentiating between the two terms which are frequently used synonymously—"early glaucoma" and "mild glaucoma." Only after prolonged observation can one be certain that a case belongs to the mild group.

FAMILY 9.—Armen has chronic simple glaucoma, which was discovered after serious contraction of the fields had already developed. Ilona his niece, had an acute attack in her right eye while in the hospital, awaiting sympathectomy for hypertensive vascular disease. The other eye reacted positively to the lability test and is being treated prophylactically at another clinic.

FAMILY 10.—Lottie has chronic simple glaucoma of the right eye and chronic congestive glaucoma of the left eye. The disease is mild, but the fields showed early involvement of the central area. Her sister has the syndrome of recurrent glaucomatocyclitic crises in the left eye. This disease is characterized by recurring attacks of unilateral glaucoma, associated with mild cyclitic signs, and has been described elsewhere.[66]

FAMILY 11.—Ralph is the only one of 4 siblings to have glaucoma. His mother, 4 of her brothers and 1 of her sisters had the disease. Ralph's disease began as asymptomatic glaucoma simplex, but subacute congestive attacks developed after the institution of pilocarpine therapy.

FAMILY 12.—Kurt has asymptomatic chronic simple glaucoma. He has myopia of about 6 D. in each eye. His mother and a second cousin also had the disease. After bilateral cyclodialysis in 1936, the tension of the right eye became subnormal, while the left eye continued to have a high normal tension; yet the loss

66. Posner, A., and Schlossman, A.: Recurrent Unilateral Glaucoma with Mild Cyclitic Symptoms, Arch. Ophth. **39**:517 (April) 1948.

of field has been the same in the two eyes. The occasional use of 10 per cent phenylephrine hydrochloride (neo-synephrine hydrochloride®) in the left eye enhances the effectiveness of pilocarpine.

FAMILY 13.—Reva has chronic simple glaucoma of the right eye and chronic congestive glaucoma of the left eye. Anna has chronic congestive glaucoma of the right eye and acute congestive glaucoma of the left eye. Reva's left eye has glaucoma-free intervals, but the pupillographic curve during such an interval showed a curve for both eyes similar to that found for primary glaucoma. Anna's right eye also has glaucoma-free intervals. Both sisters have diabetes, arteriosclerosis and cataracts. Reva has been followed for nine years and Anna for twenty years.

FAMILY 14.—Ruth has asymptomatic chronic simple glaucoma of both eyes. The disease was discovered during routine examination, which was made because of the family history. Her mother, 3 of her sisters and 1 brother have the disease.

FAMILY 15.—Edith had onset of bilateral chronic simple glaucoma at the age of 78. In 1 of her brothers and in 1 sister glaucoma developed at the ages of 55 and 45, respectively. All the affected siblings were childless.

FAMILY 16.—Lena had acute congestive glaucoma of the right eye. The left eye remained normal until her death, seventeen years later. Her 2 sisters had glaucoma. However, their children, all of whom are over 40, are free from the disease.

FAMILY 17.—Nicholas has mild chronic congestive glaucoma of the right eye. His mother had an attack of acute glaucoma at the age of 80, after the instillation of atropine for treatment of cataract. There are no other cases of glaucoma in the family.

FAMILY 18.—Abraham has bilateral chronic simple glaucoma. One sister and his paternal grandfather's brother had the disease.

FAMILY 19.—Herbert had onset of bilateral chronic congestive glaucoma at the age of 25. In his mother the disease appeared at the age of 50. This pedigree shows anticipation.

FAMILY 20.—Two sisters, Fannie and Minnie, have bilateral chronic simple glaucoma. The third sister is normal. Their father had onset of glaucoma at the age of 75. This pedigree shows anticipation with respect to adult glaucoma.

FAMILY 21.—Two sisters, Gussie and Norma, have mild glaucoma. Norma has chronic simple glaucoma of the left eye, but pupillographic studies show a similar curve for the two eyes. Gussie has chronic simple glaucoma of the right eye and chronic congestive glaucoma of the left eye. The onset in the right eye was eleven years later than that in the left eye. Norma has been followed for four years and Gussie for nine years.

FAMILY 22.—Marcus has asymptomatic bilateral chronic simple glaucoma. His mother had the same disease.

FAMILY 23.—In Renate acute glaucoma of the left eye developed at the age of 68 after facial erysipelas. Two of the patient's sisters, as well as their grandmother, have the disease.

FAMILY 24.—Sonja has bilateral congestive glaucoma of a mild form. Her mother had glaucoma. The patient and several other members of her family have hypertensive vascular disease.

FAMILY 25.—Solomon has bilateral chronic simple glaucoma. His brother also had the disease. His son, who is 51 years of age, does not have glaucoma.

FAMILY 26.—Bella had bilateral chronic congestive glaucoma, while her niece Bessie had acute congestive glaucoma in the left eye and chronic congestive glaucoma in the right eye.

FAMILY 27.—Mollie has bilateral chronic simple glaucoma. The right eye became blind after iridencleisis. In this respect, her case is similar to the 2 cases described in family 7. Her brother also has glaucoma.

FAMILY 28.—Two first cousins had monocular chronic congestive glaucoma. In each case the right eye was affected and the glaucoma ran a mild course. Both the patients had hypermetropia of a high degree. Regina was followed for twelve years and Celia for five years. The striking similarity between these 2 cases is added evidence of a genetic basis of the disease in the two cousins.

FAMILY 29.—Two first cousins had bilateral chronic simple glaucoma.

FAMILY 30.—Two first cousins have congestive glaucoma. Abraham had an acute attack in his left eye, but deep cupping was already present—evidence of a preexisting asymptomatic glaucoma simplex in that eye. Rose has chronic congestive glaucoma in the left eye. The right eye remained normal until instillation of 0.5 per cent homatropine hydrobromide precipitated an acute congestive attack six years after the onset of glaucoma in the other eye.

MECHANISMS OF HEREDITY

The pedigrees reported in this paper, as well as those found in the literature, should leave no doubt in one's mind as to the familial nature of a certain proportion of cases of glaucoma. Surely, the incidence of glaucoma in these families is far greater than that in the general population. The presence of the same disease in two or more generations of the same family is evidence that heredity plays an important role in the pathogenesis of glaucoma. Even the occurrence of the disease in two or more members of the same generation is presumptive evidence of a hereditary tendency. The chances of glaucoma occurring sporadically in more than one member of a family similar in size to those reported in this paper are negligible.

The fact that a condition becomes manifest late in life, as is the case with glaucoma, is not a valid argument against its being considered hereditary. Through his studies on identical twins, Vogt [67] produced conclusive evidence of the hereditary nature of cataract and other senile conditions. What is more, he showed that twins exhibit a striking similarity in the appearance of these conditions as seen with the slit lamp.

According to the modern concepts of heredity, the gene is the unit of inheritance. The genes occupy more or less fixed positions in the chromosomes. The latter occur in homologous pairs in the cells of the body. One member of each pair is derived from the father and the other from the mother. Only 2 of 48 chromosomes form a nonhomologous pair. These are the X and Y chromosomes, which carry the sex-

67. Vogt, A.: Lehrbuch und Atlas der Spaltlampen-Mikroskopie des Lebenden Auges, Zurich, 1942, vol. 3, pp. 933-949.

linked genes. The X chromosome carries a full complement of genes, while the Y chromosome carries relatively few.

There are three main types of heredity: dominant, recessive and sex-linked. In dominant heredity, it is necessary for only one pair of genes to carry the defect in order for the latter to become manifest. If a person who has a dominant defect marries a normal person, 50 per cent of the progeny, statistically speaking, will inherit the defect (fig. 1). Such affected parents and their affected offspring are heterozygous because the two homologous genes are not alike; one carries the trait and the other is free from it. If two such heterozygous persons mate, 75 per cent of their children will show the trait. One-half the offspring will be heterozygous for the defect; one-fourth will be homozygous, and the remaining one-fourth will be normal. The homozygous offspring

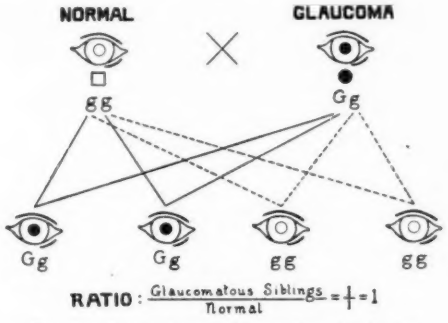

Fig. 1.—Theoretic ratio of complete dominance.

are those who carry two defective genes—one derived from the father and one from the mother.

In recessive heredity, the trait or disease does not become manifest unless both genes carry the defect. In other words, it occurs only in persons who are homozygous. Thus, many persons in the general population may carry the recessive gene for generations; yet the disease may become manifest only if one of these persons marries another person who carries the same gene.

Our family trees and all but 2 pedigrees in the literature appear to show a dominant heredity. For this reason, it is fitting to discuss more fully the mechanisms involved in this form of inheritance. Theoretically, if complete dominance were present, at least 1 case of glaucoma should occur in each generation. It has been shown, however, not only in human genetics but also in well controlled animal experiments, that a defect may fail to appear in one generation but may continue to manifest itself as a dominant in subsequent generations. This phenom-

enon of skipping a generation is known as "lack of penetrance." This means that the disease fails to express itself in the soma, even though the gene is present in the germ cell; this presence is evident from the transmission of the disease to the succeeding generation. It is possible for glaucoma to occur in such a mild form that it can be detected only by use of pupillography, by provocative tests, or by prolonged periods of observation. The differences in the severity of the disease may be accounted for in some cases by differences in the "expressivity" of the gene. The appearance of glaucoma late in life may be regarded as demonstrating a relative lack of expressivity. Since glaucoma may

Data for Determination of Penetrance

Family No.	Total No. Siblings	Siblings with Glaucoma	Sibships with No Glaucomatous Parent	Sibships with One Glaucomatous Parent	Sibships with One Glaucomatous Parent and No Glaucomatous Children
2	9	4	..	1	..
3	20	7	1	3	..
4	13	4	..	2	..
5	3	3	..	1	..
6	4	3	..	1	..
7	3	3	..	2	..
8	5	2	..	1	1
9	3	3	1	1	..
10	5	2	..	1	1
11	6	1	..	1	1
12	3	2	1	1	..
14	3	4	..	1	..
15	10	3	1	..	..
20	3	2	..	1	2
24	5	2	1	1	..
28	5	1	..	1	..
Total	125	46	5	20	5

begin as late as from 70 to 80 years of age, it is impossible to be certain whether a person who dies at an earlier age would have manifested the disease. Since the concepts of expressivity and penetrance, at least as applied to glaucoma, may imply merely quantitative differences, they cannot be sharply differentiated from each other.

The genetic approach to the study of disease in human beings is complicated by the small size of the average pedigree and by variability in penetrance. According to Gates,[68] "in short pedigrees . . . the real method or methods of inheritance may emerge only after comparing several pedigrees of the same condition." Following the suggestion

68. Gates, R. R.: Human Genetics, New York, The Macmillan Company, 1946, vol. 1, p. 4.

of Dr. M. Demerec and Dr. H. B. Newcombe, of the Carnegie Institution of Washington, department of genetics, we have pooled our material for statistical purposes, in order to gain better insight into the mechanisms of heredity.

The table shows the method used for determining the degree of penetrance of the gene for glaucoma. Only 16 pedigrees contained sufficient data to be used for this purpose. Even in these family trees, we discarded those sibships in which information on the condition of the parents' eyes was indefinite or in which the parent died before the age of 40. We also discarded those sibships in which the children did not reach the age of 40, except when one of the members manifested glaucoma at an earlier age.

Alternative methods of arriving at penetrance values are compared. In dominant heredity, one must assume that nearly all the affected persons are heterozygous. For this reason, the expected ratio of glaucomatous to normal sibling should be 1:1 (fig. 1). If the number of affected persons is significantly less than 50 per cent, the difference may be regarded as lack of penetrance. Of a total of 125 siblings, there were 46 siblings with glaucoma. If penetrance were 100 per cent, the expected number of glaucomatous persons would be 62. The ratio of 46:62, or 74 per cent, denotes the average penetrance at the age of 40 (fig. 2).

The other method of studying penetrance is a comparison of the number of sibships with one glaucomatous parent and the number neither of whose parents has glaucoma. If penetrance were 100 per cent, no generation should entirely escape the disease. If neither parent has glaucoma and the disease appears in 2 of the children, one assumes that the germ plasm of one of the parents contains the gene for glaucoma. The totals in the table show 20 sibships in which one parent had glaucoma, as compared with 5 sibships in which neither parent had glaucoma. Thus, 20 of 25 sibships showed complete penetrance. This makes the average penetrance for the group 80 per cent (fig. 2).

Both these methods probably overestimate penetrance. While our pedigrees include only the families with 2 or more affected members, there undoubtedly are families with one affected member in which other members are genetically glaucomatous without exhibiting the disease clinically. Even though the two methods used yielded similar values for the degree of penetrance in cases of hereditary glaucoma, it should be remembered that these figures (74 and 80 per cent) are, at best, rough estimations because of the small number of cases available for this study.[69]

69. For this reason, no correction was made for random sampling, such as the exclusion of the prepositus patient (the one who brought the family to the attention of the physician).

The lack of penetrance of the gene has definite clinical implications in the study of the behavior of glaucoma. It shows, by the genetic method, that a person may fail to show any clinical manifestations of the disease and still be genetically glaucomatous.

One of the pedigrees (family 8) shows probably a dominant mutation. The father of Lottie and John was the only sib with glaucoma

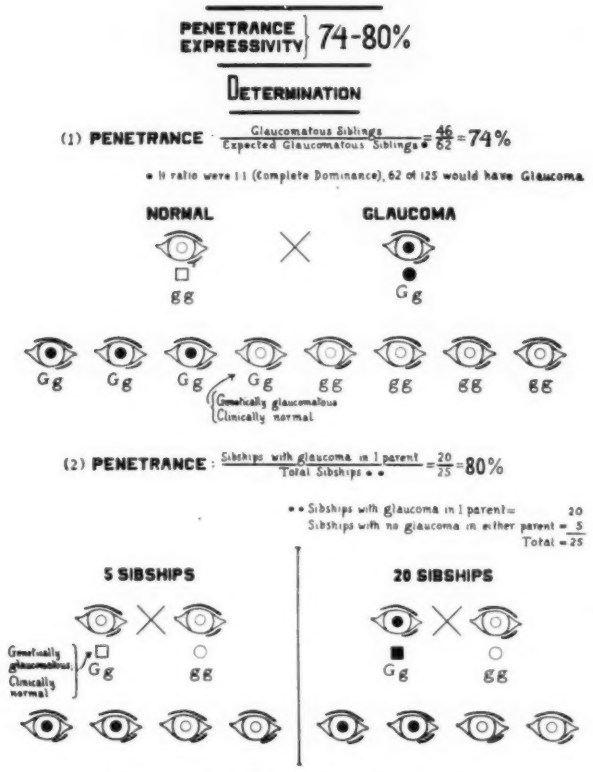

Fig. 2.—Actual ratio of incomplete dominance.

among 10 brothers and sisters. His father and mother lived to be over 90 years of age and were normal. The chances of dominant heredity when only 1 of 10 siblings is affected is less than 1 per cent. We may assume, therefore, that a gene was changed in such a way that it now transmits glaucoma in a dominant manner.

In family 1, there was a marriage between two persons in whom glaucoma developed in later life. Up to the present, 3 of their 6 children have exhibited the disease. If both parents are heterozygous for glaucoma, the expected ratio is 3 glaucomatous children to 1 normal child. Some of the affected members of the third generation are probably homozygous for the disease. Since all children of homozygous parents should inherit glaucoma, it will be interesting to watch their progeny (generation 4).

Families 28, 29 and 30 show glaucoma in 2 first cousins. Family 30 is the only one for which we have an adequate pedigree. The others were included because the clinical course of the affected patients was followed for a long time. It is impossible to draw conclusions from such incomplete material. The occurrence of glaucoma in family 30 may represent dominant heredity with a very low penetrance, or the inheritance may be recessive. This strongly suggests the possibility of more than one type of inheritance in glaucoma, since the chance of coincidence is negligible. In discussing the role of dominant and recessive heredity in evolution, Morgan [70] stated that there is no sharp contrast between dominant and recessive genes.

> Many genes classified as recessive produce some effect in hybrid combination on the character most affected . . . it follows that there may be no essential difference between the kinds of genes in question.

This raises the question of the possibility of recessive inheritance for glaucoma in general. The literature does not enlighten one on this point. From small pedigrees it is impossible to draw any conclusions about recessive inheritance, unless consanguinity is present. In order properly to study this type of heredity, one must investigate large numbers of members of a family and compare the incidence of glaucoma in this family with that in the general population.[71] Sufficient data are not available to justify any conclusions as to the role of recessive heredity in glaucoma in general. In recessive heredity, the gene may become widespread in the population without manifesting the disease except as a result of chance mating of carriers (heterozygous persons). This may be one way of accounting for sporadic cases. For the sake of speculation, let us asume, for the moment, that all glaucoma is hereditary. If the incidence of the disease is 0.25 per cent of the general population, then 9.5 per cent of the entire population would carry one gene for glaucoma (heterozygous). Thus the possibility of chance matings is not inconsiderable.

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70. Morgan, T. H.: Evolution and Genetics, Princeton, N. J., Princeton University Press, 1925, p. 15.

71. Reudin, E.: Zur Vererbung und Neuentstehung der Dementia praecox, Berlin, Julius Springer, 1916; in Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie, 1916, no. 12.

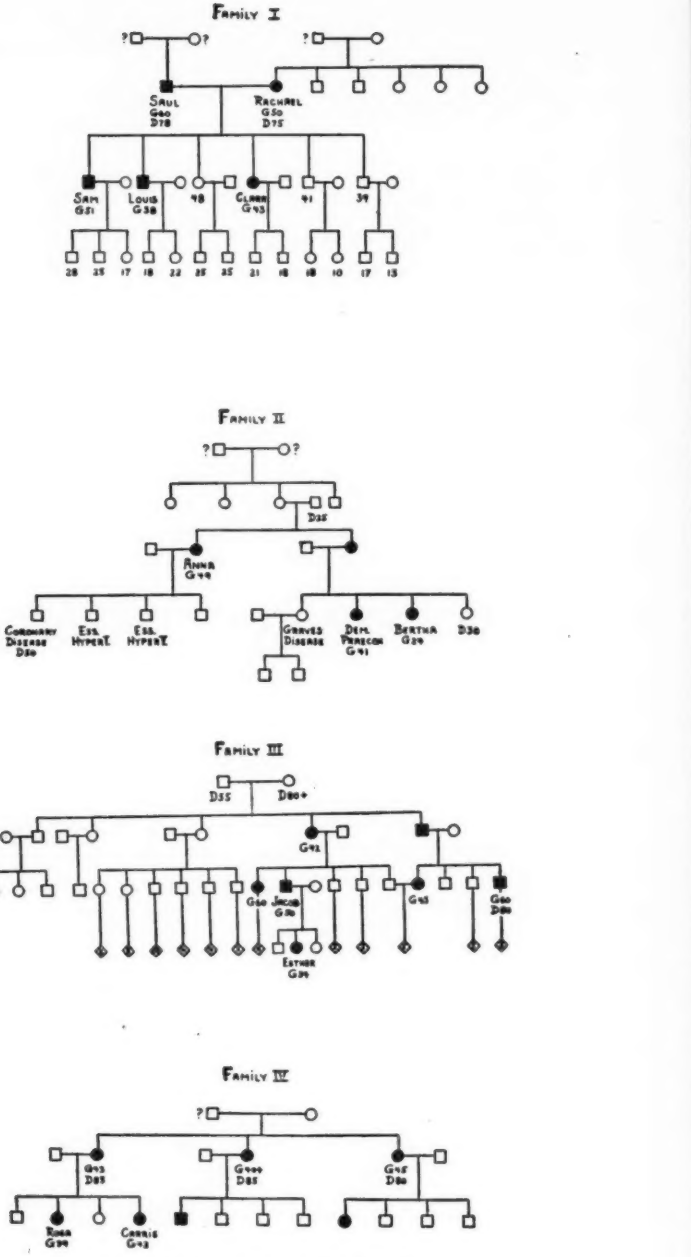

Fig. 3.—Pedigrees for families 1 to 4.

COMMENT

The group of hereditary glaucoma forms a representative cross section of cases of the disease in general. In several instances the disease began as chronic simple glaucoma but was complicated by congestive attacks after prolonged use of miotics. Many gradations in severity were encountered—from those cases in which the disease remained mild over many years to those in which it resulted in blindness in a relatively short time.

Of 373 patients with glaucoma, 51 had demonstrable hereditary tendencies—an incidence of 13.7 per cent of all the patients with glaucoma available for our study. Of 91 eyes, 52 had chronic simple glaucoma, 10 had chronic congestive glaucoma and 14 had acute glaucoma.

A review of the case histories reveals that in many families there were similarities in the behavior of the disease with respect to type, refractive error, severity and response to surgical treatment. In 4 families the glaucoma was of the chronic simple type in all members examined. In 2 families all members had chronic simple glaucoma, but congestive attacks occurred in some of them. In 3 families all members had congestive glaucoma. One of these (family 6) is interesting because all 3 sisters had acute congestive glaucoma, although the first attack occurred at 17, 39 and 71, years of age respectively. In several families, however, the type of glaucoma differed in the different members.

The refractive error was similar in 9 families and significantly different in 4 families. This group affords a rare opportunity for the study of mild glaucoma, since some of the cases would not have been discovered were it not for the presence of glaucoma in other members of the family. In families 4, 5 and 8, the glaucoma was exceptionally mild in all but 1 member. It ran a moderately severe course in all the members of families 3 and 19. In family 7, the glaucoma displayed an unusually severe course in the affected eyes of both members. Moreover, both father and daughter reacted poorly to operation on the iris. In family 6, 3 of the 5 affected eyes (belonging to 3 different members) had to be enucleated because of poor response to surgical procedures on the iris.

These examples are at least suggestive that not only the disease but also the pattern of its behavior may be influenced by heredity in some cases. Since the knowledge of a case history of one member may serve as an aid in the treatment of another affected member, it is advisable for the opthalmologist to acquaint himself, whenever possible, with the histories of all members of the family who have the disease. This is especially important when one member has shown dis-

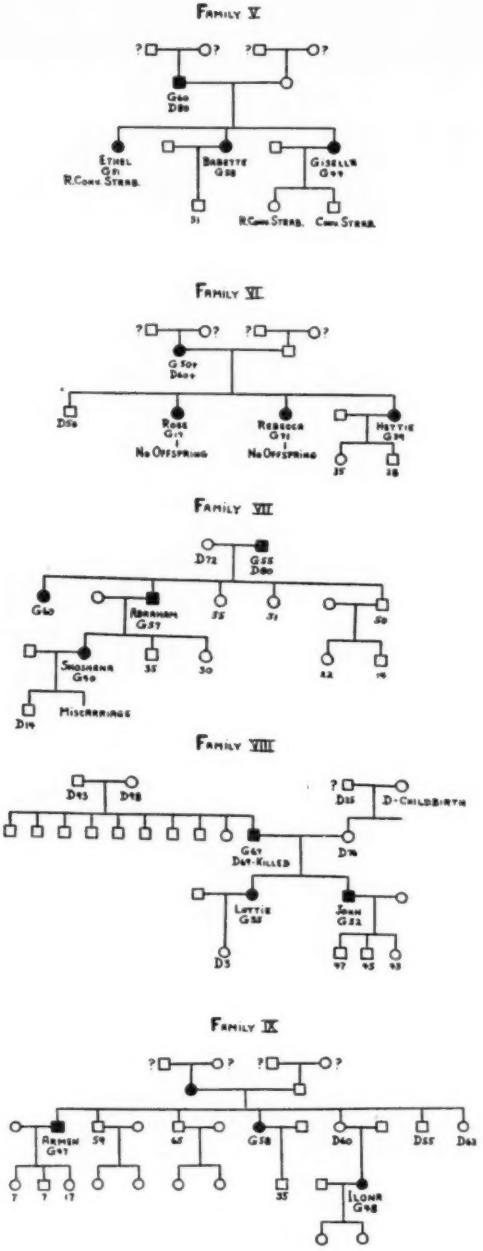

Fig. 4.—Pedigrees for families 5 to 9.

astrous results following surgical procedures on the iris. In such a case it may be advisable to use cyclodialysis as the operation of choice. If the disease has proved mild in other members of the same family and the course of the patient's glaucoma appears to be similar, the physician may reassure his patient that his disease will probably follow a similar pattern.

The hereditary approach may help to bring primary glaucoma into relation with other types of glaucoma. Ever since von Graefe called attention to "amaurosis with excavation," the role of glaucoma without hypertension has been a subject of controversy. Elschnig [72] reported a family in which 2 first cousins had glaucoma without hypertension, while an uncle suffered from glaucoma with hypertension. Recently, Sjögren [73] has attempted to show, on a clinical basis, that simple glaucoma displays wide variations in symptomatology, and that glaucoma without hypertension may be regarded as one type of primary glaucoma. Glaucoma which develops after cataract extraction should not, as a matter of course, be classified as secondary. We have reported several cases elsewhere [51] in which a positive result in the provocative tests in the opposite eye or the occurrence of primary glaucoma in the eye not operated on proved that the disease was probably primary glaucoma. The father of one of our patients with primary glaucoma (N. W.) had ocular hypertension following an uncomplicated cataract extraction. A knowledge of the family history should be helpful in evaluating such a case. Certain cases of recurrent unilateral glaucoma with mild cyclitic signs, a condition which we have called the syndrome of recurrent glaucomatocyclitic crises, [66] probably form an intermediate group between primary and secondary glaucoma. Its relation to primary glaucoma is further evidenced by the pedigree of family X. Of 2 affected sisters, 1 has primary glaucoma and the other the syndrome of glaucomatocyclitic crises. Another patient (A. S.) with the latter disease has an aunt with primary glaucoma. The relation of retinitis pigmentosa to primary glaucoma is obscure. There are several pedigrees in the literature in which the association appears. Blessig [74] reported a sibship of 9 members of whom 2 sisters had chronic simple glaucoma alone, while 2 brothers and 1 sister had pigmentary degeneration without ocular hypertension. We have a patient with retinitis pigmentosa and glaucoma of the congestive type.

72. Elschnig, A.: Glaucoma Without Hypertension and Hypertension Without Glaucoma, Ztschr. f. Augenh. **52**:287-296, 1924.

73. Sjögren, H.: A Study in Pseudoglaucoma, Acta ophthal. **24**:239-294, 1946.

74. Blessig, E.: Alternating Occurrence of Glaucoma Simplex and Retinitis Pigmentosa in a Series of Siblings, St. Peterberg. med. Wchnschr. **21**:105-106, 1901.

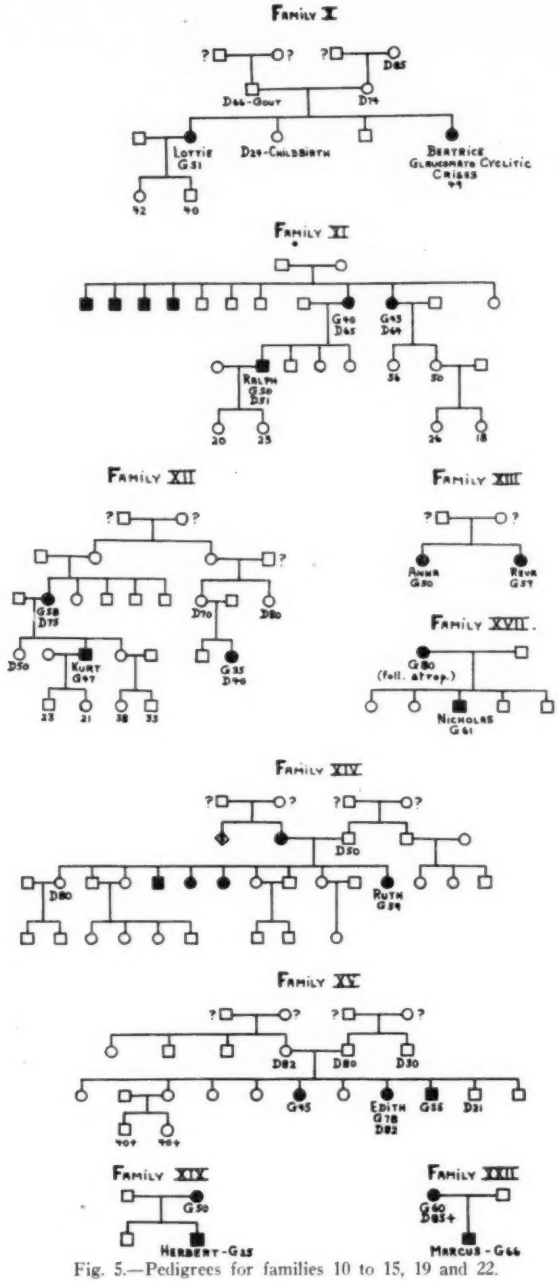

Fig. 5.—Pedigrees for families 10 to 15, 19 and 22.

Two of her sisters have retinitis pigmentosa, but only 1 of them has glaucoma. From a genetic point of view, these examples show that primary glaucoma cannot be sharply differentiated from secondary glaucoma on a clinical basis alone. This evidence is in agreement with the everyday experience of the ophthalmologist.

The occurrence of hydrophthalmos and primary glaucoma in the same family has been reported in 4 pedigrees from the literature. We have previously stated our reasons for believing that the two diseases are not related. It is possible, however, that two clinically different diseases may be associated genetically by linkage of the genes. This may also be the case with retinitis pigmentosa and strabismus.

Among constitutional diseases, hypertensive vascular disease and diabetes are those most commonly associated with glaucoma. Elwyn [75] pointed out that in all three diseases there is a disturbance of the regulatory function. In family 2, 4 members have glaucoma; 2 have hypertensive vascular disease; 1 has coronary disease; 1 dementia precox, and 1, toxic goiter. Another pedigree, family 13, shows 2 sisters with glaucoma and diabetes. Many pedigrees of patients from the nonhereditary group exhibit a strikingly large incidence of metabolic disorders among the nonaffected members. It is possible that the gene for glaucoma is somehow related to the gene or genes for other regulatory diseases.

It is difficult to determine the exact manner in which heredity affects the eye. Many anatomic variations and abnormalities have been implicated. Some of them were mentioned in a previous section. The belief is prevalent that hypermetropia is a predisposing factor in glaucoma. While it is true that hypermetropia may be inherited, we have shown that the refractive errors found among patients with glaucoma follow the same distribution as those in the general population.[51] Holst [76] supported this point of view.

It was previously shown that some persons are genetically glaucomatous but show no clinical manifestations of the disease. They may have glaucoma at some future time of life, either spontaneously or as the result of a provocative factor, such as instillation of atropine, cataract extraction or emotional disturbances. From this point of view, their normal state may be regarded as a preclinical stage. It would be interesting to find tests which would detect patients who are potentially glaucomatous while they are still clinically normal. Pupillography promises to be of great value in this respect for it enables one to evaluate

75. Elwyn, H.: The Pathogenesis of Chronic Simple Glaucoma, Arch. Ophth. **19**:966-1008 (June) 1938.

76. Holst, J. C.: A Statistical Study of Glaucoma, Am. J. Ophth. **30**:1267-1276, 1947.

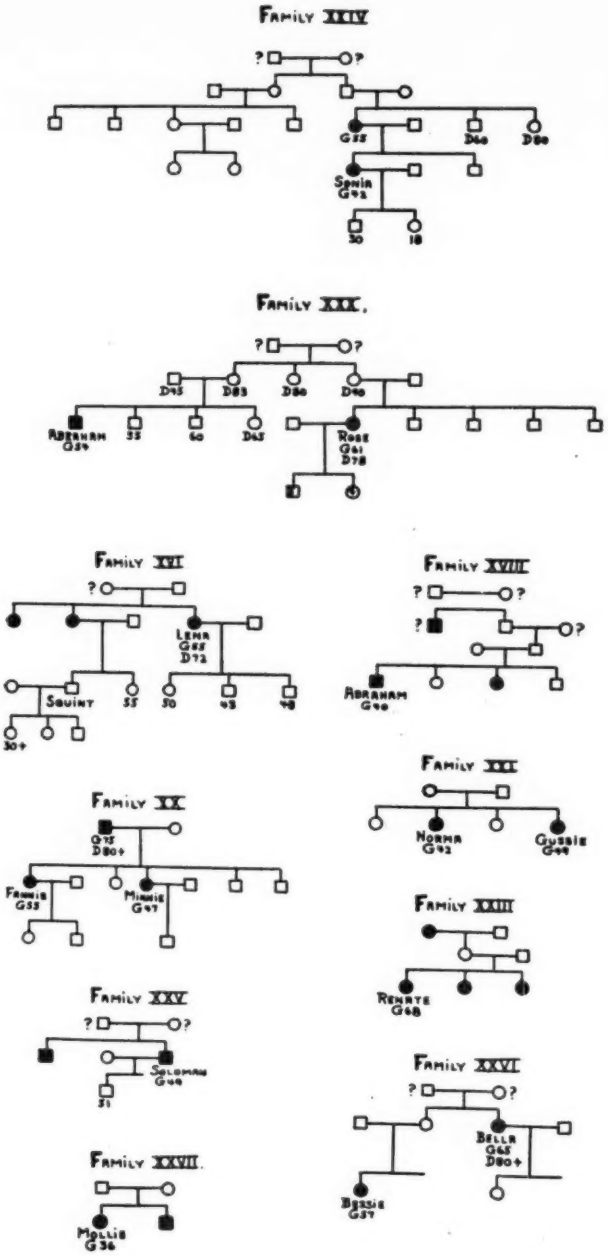

Fig. 6.—Pedigrees for families 24, 30, 16, 18, 20, 21, 23, 25, 26 and 27.

the state of the autonomic nervous system, especially the hypothalamic center. In all the cases of primary glaucoma thus far studied, a pupillographic curve had certain definite characteristics.[64] Fourteen normal relatives of glaucomatous patients were subjected to pupillographic studies. Three of these persons showed curves similar to those found in cases of primary glaucoma, while all other tests gave negative results. Further work along this line is now in progress. It is possible that the inherited factor is a disturbance in the central autonomic nervous system.

The mechanism of heredity as related to our pedigrees has already been discussed. The role of genetics among the sporadic cases cannot be entirely ignored. Considering the possibility of low penetrance and low expressivity, it is not unlikely that in some of the spordic cases the disease is also hereditary. It is well known that the same disease may be transmitted in dominant, recessive and sex-linked manner. This is true of retinitis pigmentosa and Leber's disease (hereditary optic atrophy). Recessive genes for a given trait may become widespread in the general population without the trait becoming manifest. The occurrence of sporadic cases may result from the mating of two persons who carry recessive genes.

In view of the extreme degree of hybridization of the human species, it is impossible to make any predictions as to the heredity in a specific case of glaucoma. From the eugenic standpoint, one may, however, feel justified in advising a patient with glaucoma in whose family the disease shows dominant heredity against marrying into another family with glaucoma.

For a better understanding of the mode of transmission of glaucoma, it is essential to have a large series of good pedigrees. The technic of taking pedigrees is simple. It is important to obtain the total number and ages of all the siblings in each generation, the age of onset of the disease and the age of death of the deceased members. We regret that some of our pedigrees are incomplete. Since some of the patients were not available for questioning during the past year, a few of these family histories were obtained indirectly through the case records. We hope to complete these pedigrees in the near future.

Patients are acutely aware of the hereditary potentialities of diseases. It behooves the physician to give serious attention both to the psychologic and to the ophthalmologic aspects of the patient's problem. Provocative tests and pupillography, when feasible, are of great value, since a negative result helps to reassure the patient and a positive result means an early diagnosis.

SUMMARY

Heredity plays a role in the pathogenesis of glaucoma. Fifty-one, or 13.7 per cent, of 373 unselected cases from private practice showed familial tendencies.

In most families the disease follows a similar course in the various affected members.

All the pedigrees show dominant heredity, except for 1, in which it may be recessive. Some sporadic cases may, on careful analysis, prove to be hereditary.

The genetic approach may be an aid in the early recognition of glaucoma and in the study of the preclinical and mild phases of the disease.

The pedigrees of all but 2 of the families (28 and 29) are included.

EXPERIMENTAL STUDIES OF INCLUSION BLENNORRHEA

Isolation of a Virus

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INCLUSION blennorrhea is a disease of the conjunctiva related to cervicitis in the female and urethritis in the male; it can be considered a virus venereal disease. The disease occurs most commonly in newborn infants but is also observed in adults. The adult gets the disease by coming in contact with the virus from the urethra or the cervix either by direct contamination or in swimming pools. The clinical manifestations of the disease have been reviewed repeatedly,[1] and it is the purpose of this report to present a study of the probable etiologic agent as a virus rather than to describe further the clinical syndrome.

Thygeson [2] has shown that the virus of inclusion blennorrhea is morphologically identical with the virus of trachoma except that the matrix of the inclusions of trachoma stain more uniformly with iodine than those of inclusion blennorrhea. The viruses of these two diseases are similar morphologically to the viruses of lymphogranuloma venereum and psittacosis. Macnie [3] and others have shown that the virus of lymphogranuloma venereum can involve the eye, but thus far no reports can be found that psittacosis has ever invaded this structure.

Dr. Phillips Thygeson and Dr. Murray Sanders made valuable suggestions and criticisms.

This paper was submitted as a candidate's thesis for membership in the American Ophthalmological Society June 1947.

These studies were conducted under several grants. The major portion of the work was done under a grant from the Knapp Memorial Fund, at the Department of Ophthalmology, Columbia University College of Physicians and Surgeons. Some of the biopsies were conducted under a grant from the John and Mary R. Markle Foundation at the Department of Ophthalmology, State University of Iowa College of Medicine, Iowa City.

1. O'Brien, C. S., and Allen, J. H.: Allergic Keratoconjunctivitis, Tr. Am. Ophth. Soc. **40**:170, 1942. Braley, A. E.: Am. J. Ophth. **21**:1203 (Nov.) 1939. Thygeson, P., and Mengert, W. F.: Virus of Inclusion Conjunctivitis: Further Observations, Arch. Ophth. **15**:377 (March) 1936. Lindner, K.: Arch. f. Ophth. **78**:245, 1911. Howard, W. A.: J. Pediat. **12**:139 (Feb.) 1938.

2. Thygeson, P.: Am. J. Ophth. **17**:1019 (Nov.) 1934; **14**:455 (July) 1938.

3. Macnie, J. P.: Ocular Lymphogranuloma Venereum, Arch. Ophth. **25**: 255 (Feb.) 1941.

An attempt was made to grow the virus by several biologic methods and to reproduce the disease. I was unable to fill these requirements, but a great deal was learned concerning the virus. Although most of the data presented here are negative, it is felt that the results of this study give some indication of the problem and may be an aid to further investigation.

ATTEMPTS TO GROW THE VIRUS

All viruses apparently are obligatory parasites and require living cells for propagation. Most of them have an affinity for certain cells in the body in order to propagate. The virus of lymphogranuloma venereum seems to grow best in the cells of the reticuloendothelial system, but it can be adapted to the mouse brain and also to the yolk sac of the developing hen's egg. The viruses of vaccinia and herpes appear to be predominantly epitheliotrophic, but these also can be adapted to other cells.[4] The viruses of inclusion blennorrhea and trachoma appear to differ slightly in their cell specificity. The virus of inclusion blennorrhea seems to be predominantly present in the epithelium of the lower conjunctival sac and involves also a narrow zone in the cervical epithelium.

As has been mentioned before, the virus of inclusion blennorrhea is similar to the viruses of trachoma, lymphogranuloma venereum and psittacosis. All four of these viruses are similar in several respects: (1) They all stain easily by the Giemsa method; (2) all form distinct inclusion bodies; (3) all occur in two forms, the elementary body form and the initial body form; (4) all seem to have fairly distinct tissue specificity in the human subject; (5) all, with the possible exception of the virus of psittacosis, are sensitive to the sulfonamide drugs, and (6) all fall in a class which seems to be between true viruses, such as those of herpes simplex, vaccinia and poliomyelitis, and the rickettsias. With all these similarities, it would appear that the viruses of both trachoma and inclusion blennorrhea would follow the same pattern as lymphogranuloma and psittacosis. The virus of lymphogranuloma[5] grows well in the yolk sac of the developing chick embryo, on the chorioallantoic membrane and in tissue culture; however, in many instances in which the virus is obtained from the human patient it must be adapted to its new environment. This may require mutation. With these facts in mind, I then conducted experiments with inclusion blennorrhea.

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4. Rivers, T. M., and others: Problem and Trends in Virus Research, University of Pennsylvania Bicentennial Conference, Philadelphia, University of Pennsylvania Press, 1941.

5. (*a*) Rake, G.; McKee, C. M., and Shaffer, M. F.: Proc. Soc. Exper. Biol. & Med. **43**:332 (Feb.) 1940. (*b*) Sanders, M.: J. Exper. Med. **71**:113 (Jan.) 1940.

METHODS AND PROCEDURES

Epithelial scrapings obtained with a platinum spatula from adults or infants with inclusion blennorrhea were suspended in isotonic sodium chloride solution U. S. P., neutral nutrient broth, serum ultrafiltrate and sterile distilled water. This material was then (1) inoculated on the chorioallantoic membrane of the developing hen's egg, (2) injected into the yolk of the developing hen's egg, (3) inoculated into fluid tissue cultures and (4) inoculated in normal conjunctival epithelial cells in tissue culture. Biopsy specimens from babies with inclusion blennorrhea were also grown in tissue culture by the Carrel technic.

Egg Inoculations.—In order to inoculate the chorioallantoic membrane, hen eggs were incubated at 38 C. for from five to nine days. A triangular window was then made through the shell over the location of the embryo. A smaller hole was made at the air sac. The air was then withdrawn from the air sac, whereupon the embryo dropped away from the shell membrane at the opening through the shell. The shell membrane was then opened with a sterile knife and the material for inoculation placed inside the shell membrane on the chorioallantoic membrane. The shell was replaced over the area and sealed with paraffin or scotch tape. Both openings in the egg were sealed. The eggs were then replaced in the incubator and opened at periods of from three days to maturity, and the chorioallantoic membrane was removed and studied for lesions. Smears of the embryo and chorioallantoic membrane were also made and stained with Victoria blue and by the Giemsa method.

The yolk sac method of egg inoculation was simpler; it consisted of making a small hole in the egg shell over the air sac and inoculating the material through this opening into the yolk sac by means of a long hypodermic needle. This inoculation was made after an incubation period of from five to nine days. The eggs were opened at periods varying from three days to near maturity, the entire egg being opened so that the embryo was isolated. The embryo was picked up and, with the yolk sac attached, was placed in a sterile Petri dish. Smears or sections, and in many instances both, were made of the embryo. The yolk sac was separated from the embryo and freed of as much yolk as possible, and smears were made of the yolk membrane. These were stained with Victoria blue and by the Giemsa method.

In an attempt to adapt the virus to both the chorioallantoic membrane and the yolk sac of chick embryos, serial passages of both were carried out. This was accomplished by removing either the membrane or the yolk sac, grinding it with a small amount of sterile saline solution and reinoculating eggs with this material. On several occasions during this serial passage, portions of the membranes were used to inoculate baboons, in an effort to determine their infectivity. Fifty-three serial passages were made of inoculated yolk sac and 23 of inoculated chorioallantoic membrane.

Inoculation of Fluid Tissue Culture.—The tissue culture used in these experiments consisted of balanced saline solution, serum ultrafiltrate and finely divided tissue. The cultures were similar to those used by Sanders [5b] in the propagation of lymphogranuloma virus. Scrapings of the conjunctival epithelium were taken directly from patients with inclusion blennorrhea and inoculated into two fluid cultures. One culture was placed in the incubator at 37 C., and the other was kept at room temperature. A moderate amount of material was removed from the culture, ground in a mortar and inoculated intracerebrally in mice and into the eyes of baboons. Cultures were checked for sterility on ordinary mediums at periodic intervals, and when a tissue culture was contaminated it was either

discarded or filtered and another tissue culture inoculated. These cultures were also passed serially; the incubator cultures were inoculated into mice at three day intervals and the room temperature cultures at five and nine day intervals. All inoculation of cultures attempted by this method failed to infect baboons and did not give rise to encephalitis in mice.

Tissue cultures were inoculated into the mice in most instances by three methods. Approximately 0.02 cc. of the tissue culture fluid was injected intracerebrally. The mice were also given from 0.05 to 0.2 cc. intraperitoneally, and about half the mice were inoculated with from 0.02 to 0.1 cc. intravenously. Each mouse was inoculated by all three methods in an effort to have as much virus as possible present at the site of inoculation in the brain. The intravenously

TABLE 1.—*Tissue Culture of Material from Inclusion Blennorrhea*

No. of Experiments	Source of Material Inclusions	Infective for Baboon	Medium		Gas	Growth and Comment
			Clot *	Fluid †		
2	Cervix	.....	C.P. 1/10	T.S. 1/2	Carbon dioxide	Epithelium and leukocytes
4	Conjunctiva of patient with inclusion blennorrhea	.....	C.P. 1/2	T.S. 1/1	None	Leukocytes
2	Conjunctiva of patient with inclusion blennorrhea	Not done	C.P. 1/2	T.S. 1/1	Carbon dioxide	Good epithelium; no inclusions
5	Conjunctiva	.....	C.P. 1/5	T.S. 1/2	Oxygen and carbon dioxide	Epithelium and fibroblasts; no inclusions
6	Cervix	.....	C.P. 1/5	T.S. 1/1	Oxygen and carbon dioxide	No growth except leukocytes; baboon inoculations
5	Conjunctiva	Not done	C.P. 1/5	T.S. 1/2	Oxygen and carbon dioxide	Epithelium, fibroblasts and leukocytes; noninfectious for baboon; transplant epithelium
6	Conjunctiva	.....	C.P. 1/3	T.S. 1/1	80% oxygen, 8% carbon dioxide	Epithelium and fibroblasts; noninfectious for baboons
2	Conjunctiva	.....	Fibrin and thrombin, T.S. 1/1		21% oxygen, 3% carbon dioxide	Epithelium — no inclusions

* C.P. indicates chicken plasma; and T.S., Tyrode's solution (modified Locke's solution containing magnesium) and serum or serum ultrafiltrate.

injected virus would probably be filtered out in the spleen or in the liver, but it was felt that some of it might reach the point of inoculation in the brain. The intraperitoneal inoculation was given because a large amount of material could be injected into the peritoneal cavity without causing too much shock to the animal.

Inoculation of Normal Conjunctival Epithelial Cells in Tissue Culture.—Normal conjunctival tissue was obtained from the operating room. This was handled under sterile conditions and after division into small pieces was placed in a Carrel flask and secured by chicken plasma. The nutrient material overlying the tissue in the flask was either normal serum or serum ultrafiltrate plus a balanced saline solution (Tyrode's). Tissue cultures were allowed to grow at incubator temperature until a fair growth of epithelium was obtained. The supernatant fluid was then removed and replaced with a solution consisting of balanced saline solution and serum ultrafiltrate to which scrapings from an eye with inclusion blennorrhea

had been added. This was allowed to remain in the incubator for from one to seven days. Some of the preparations were stained by the Giemsa method and studied for the presence of inclusion bodies, while others were removed and the material was inoculated into the eyes of baboons.

Tissue Culture of Inclusion Conjunctivitis.—Biopsies of the conjunctiva were made on patients with inclusion blennorrhea, and biopsies of cervical tissue, from mothers whose babies had inclusion blennorrhea. This tissue was handled by a method similar to that reported by Thygeson [6] with trachoma. Epithelial growth was obtained in nearly all instances. These cultures were handled in several ways. In some of them the supernatant fluid was removed and inoculated into baboons' eyes. In some the tissue was removed and inoculated into baboons' eyes after growth had been obtained. Some were stained and studied for the presence of inclusions bodies (table 1).

Variation in Tissue Culture Mediums.—Apparently, a substance present in the normal conjunctiva which made it possible for cells to be infected with the virus was not present in the tissue culture. Therefore, numerous amino acids were added to the tissue culture in order to stimulate epithelial growth and possibly supply the missing substance.

RESULTS

The direct inoculation of a chorioallantoic membrane gave entirely negative results, since no demonstrative growth of virus was obtained. On occasion, small foci could be found on the membranes which were suggestive, but when they were examined in smears microscopically no inclusions could be demonstrated by Giemsa's method or with Victoria blue.

The direct inoculation of yolk sac failed to propagate the virus, although by similar technic the virus of lymphogranuloma venereum was successfully grown. Blind passage in eggs all failed to yield the virus. The yolk sac was ground and the material inoculated into baboons' eyes. Numerous smears of yolk sacs were made and stained by the Giemsa method and with Victoria blue but failed to demonstrate the virus. The virus seems to have little or no effect on the developing hen's egg, and when allowed to do so the egg would produce a healthy chick.

The virus was not propagated in fluid tissue culture with any of the types of tissue used. Serial passage in tissue culture failed to infect baboons. No evidence could be demonstrated by the methods used that normal cells of the conjunctival epithelium grown in tissue culture could be infected by the virus of inclusion blennorrhea. Conjunctival epithelium from tissue already infected with the virus of inclusion blennorrhea did not remain infectious in tissue culture with the methods used.

Comment.—Accepted methods for propagation of the viruses of lymphogranuloma venereum and vaccinia were used in an attempt to grow the virus of inclusion blennorrhea. Thygeson [6] likewise was

6. Thygeson, P.: Cultivation of Trachomatous Conjunctival Epithelium in Vitro, Arch. Ophth. **21**:229 (Feb.) 1939.

unable to propagate the virus on the chorioallantoic membrane of developing hen's eggs. It was hoped that a mutation of the virus might occur by serial passage of eggs already infected with the virus. The results were disappointing. Since there is no morphologic similarity between the tissue of the developing chick embryo and the conjunctival epithelium, one would expect the virus of inclusion blennorrhea to be easily adapted to the conjunctiva; however, it seems strange that the virus would not grow in tissue cultures of normal conjunctival epithelium. Undoubtedly, there is some change in the epithelial cells in tissue culture which makes them noninfective. It was suspected that some material was missing from the tissue culture; and since the supernatant fluid of the tissue culture could be varied, considerable variation was made in an attempt to propagate the virus by tissue culture.

The only changes in epithelial growth that could be obtained were with the addition of two amino acids, aminoacetic acid and histidine. The best growth of epithelium in tissue culture was obtained by the addition of small quantities of aminoacetic acid. Histidine and aminoacetic acid together seemed to be somewhat better; however, numerous essential amino acids were added to tissue culture in an effort to supply the missing substance which is present in the normal conjunctiva but not in the tissue culture.

The fate of the virus after inoculation either into eggs or tissue culture is difficult to understand, for, regardless of the type of medium into which it was placed, the virus disappeared quickly. It has been found from previous experience that the virus must be transferred carefully and quickly from the patient to the conjunctiva of baboons in order to obtain a good experimental inclusion blennorrhea. Since so many epidemics of so-called swimming pool conjunctivitis have occurred, it seems likely that the virus might live longer in distilled water or tap water than in isotonic sodium chloride solution U.S.P. Therefore the virus was suspended in sterile distilled water and inoculated into eggs, tissue culture and mice, but with disappointing results.

The negative results of inoculation in epithelial growth in tissue culture is a little easier to explain; the leukocytes present in the tissue probably destroyed the virus as it escaped from the cells, so that in a short time the organism disappeared. This may play a part in the rapid deterioration of the virus once it is suspended in any medium. If the virus of inclusion blennorrhea could be obtained free from leukocytes, perhaps it would grow in tissue culture.

BLIND PASSAGE IN MICE

In a further attempt to propagate the virus of inclusion blennorrhea, blind passage of material was made in mice. The method of propagation of a virus by blind passage has been fairly widely used, especially when the virus is not easily adapted to a new medium. In many cases

in which a large amount of infected material can be injected into a nonreceptive tissue, it may be possible to adapt the virus to the new cell. It is often possible to adapt bacteria to a new medium by continual transfer, though sometimes the organism loses some of its virulence in such passage. Because of the difficulty in adapting the virus of inclusion blennorrhea to any medium except the cervix and

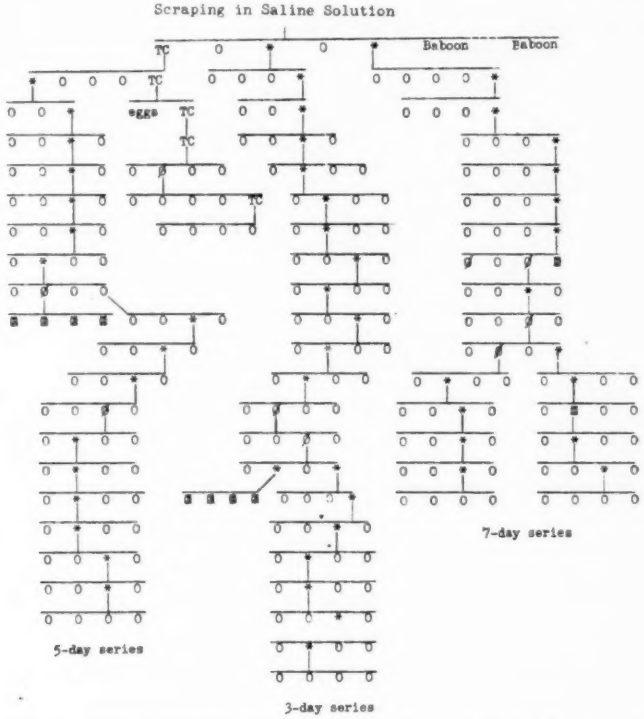

Chart 1.—Passage through mice of the inclusion blennorrhea virus from case 2.

In this chart and in charts 2 to 8, 0 means mouse watched but not passed; 0 with included cross, mouse dead; 0 with one line, mouse sick and passed, and *, mouse passed and not sick.

the eyes of baboons, it was thought that with a heavy suspension of material obtained from the human eye under sterile conditions the virus could be adapted to mouse brain by serial passage. The mice used for blind passage weighed approximately 10 to 12 Gm.

When the amount of solution was sufficient, from 3 to 5 mice were each inoculated intracerebrally, intraperitoneally and intravenously, as previously

described. The mice were divided into three groups: The first group was killed at the end of three days; the second, at the end of five days, and the third, at the end of seven days, after the original inoculation. After the brain was removed from the mouse, it was ground in a mortar under sterile conditions and mixed with 3 cc. of isotonic sodium chloride solution U.S.P., to make a heavy suspension. In some instances the suspension was injected into other mice, but usually the solution was centrifuged at low speed to draw down the larger particles of brain material. The supernatant fluid was then injected intracerebrally, intraperitoneally and intravenously into each mouse. For intracerebral injection, 3.5 per cent solution of iodine was used to prepare the skin over the skull. The mice died on injection of more than 0.02 cc. intracerebrally. Approximately 0.5 cc. was injected intraperitoneally before evidence of protein

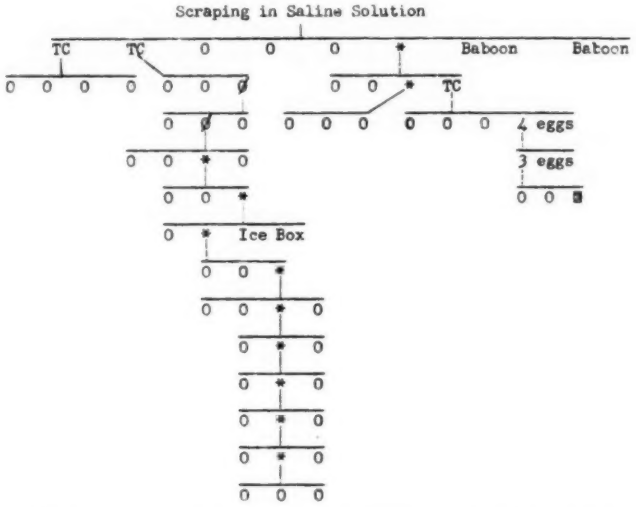

Chart 2.—Passage in mice of inclusion blennorrhea virus from case 3.

shock was obtained in the mouse. The most difficult was the intravenous injection of brain suspension. It was made into the tail vein by use of a fine needle; and 0.05 to 0.1 cc. was injected, depending on the size of the mouse, before the mouse died of protein shock.

The mice were followed carefully, and in 3 instances a possible inflammatory agent was obtained by blind passage. The reaction was characterized in the mice by roughening of the fur (which occurred on the third to the fifth day after injection), slight humping of the thoracic portion of the spine and a state of lethargy. This procedure was carried on with mice until some evidence of encephalitis could be detected; if after ten consecutive blind passages the inoculated mice showed no evidence of infection, they were discarded (charts 1-7).

In the first instance, an agent was found after four passages in the five day group. The potency of this agent could not be increased beyond 1 to 10 dilutions with isotonic sodium chloride solution U.S.P., and the agent eventually lost its potency and did not bring down mice after the tenth passage.

In 1 instance, a good deal of material was obtained from the baby and suspended in a small amount of sterile neutral broth; this was

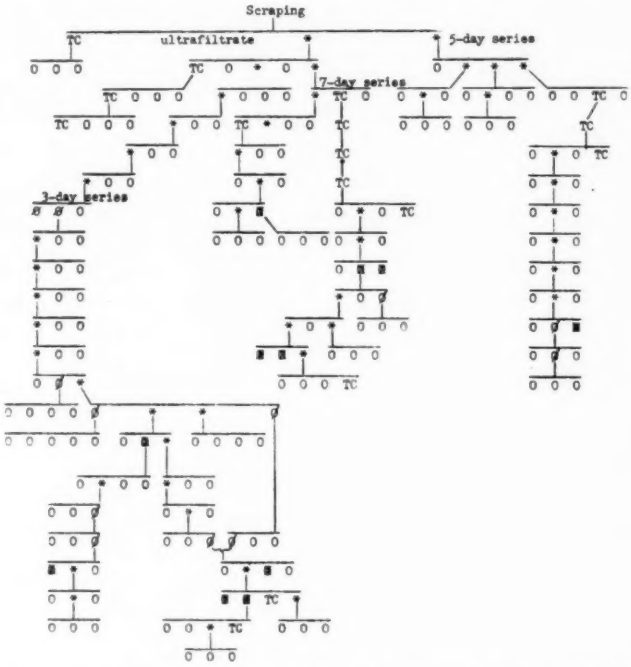

Chart 3.—Passage through mice of inclusion blennorrhea virus from case 4.

injected intracerebrally into 3 mice and passage made after incubation for three days. After the fourth blind passage, an agent was obtained which had an incubation period of five days. Passage of this material was made at four day intervals, and the potency gradually increased until a dilution of 10^{-6} was reached, which brought down all mice inoculated. This agent was considered as possible virus of inclusion blennorrhea (chart 8). On continued passage, this agent maintained a potency up to 10^{-6} and occasionally brought down mice in dilutions

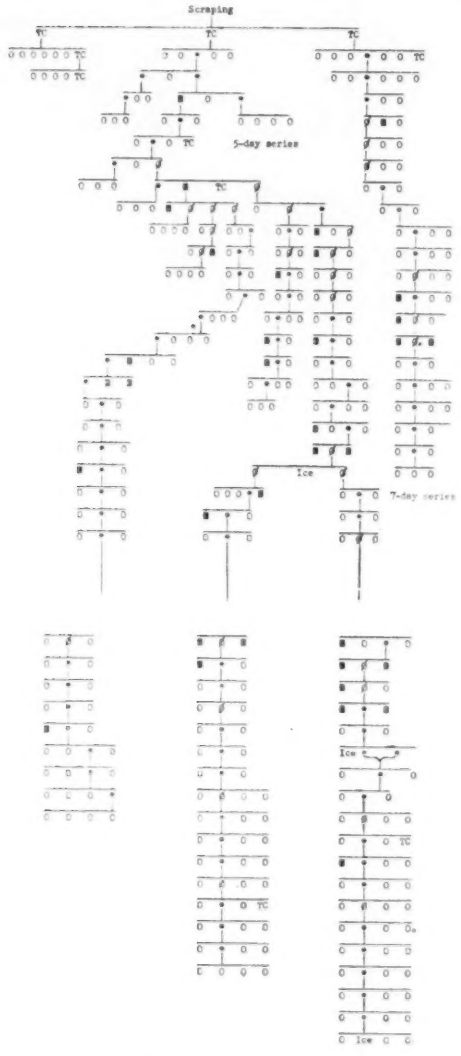

Chart 4.—Passage through mice of inclusion blennorrhea virus from case 5-T.

of $10.^{-7}$ Because of the possibility of this being the causative agent of inclusion blennorrhea, many smears were made of the mouse brain. No inclusion bodies were demonstrated, and there was no evidence of a virus being present in the smears. The smear preparations were stained with Victoria blue and methyl blue and by the Giemsa method.

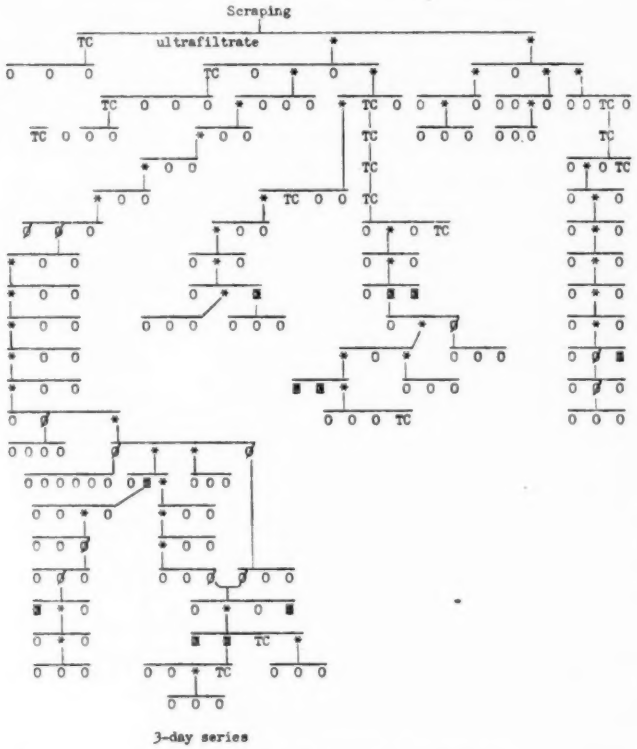

Chart 5.—Passage of material from case 4-H.

In a few smears stained with Victoria blue, some bodies were encountered, but these were thought to be artefacts. Since the agent had presumably been obtained from a patient with many free elementary bodies, it would seem proper that smears of the mouse brain should show elementary bodies. Mouse brain material suspended in isotonic sodium chloride solution U.S.P. and inoculated into the conjunctiva of dog-faced baboons gave rise to conjunctivitis in the baboons which

had an incubation period of five days. The conjunctivitis of the baboons increased, with the development of numerous follicles and a moderate amount of congestion of the blood vessels. Scrapings of the conjunctiva of the baboon failed to demonstrate inclusion bodies, and cultures of the baboons' eyes yielded no growth. Cultures of mouse brains on blood agar plates and in meat broth remained sterile. The baboons that eventually recovered from the follicular conjunctivitis within a period of six weeks to two months were inoculated with material from a baby with inclusion blennorrhea. In the eye of a baboon which had not been used before for inoculation a typical follicular conjunctivitis

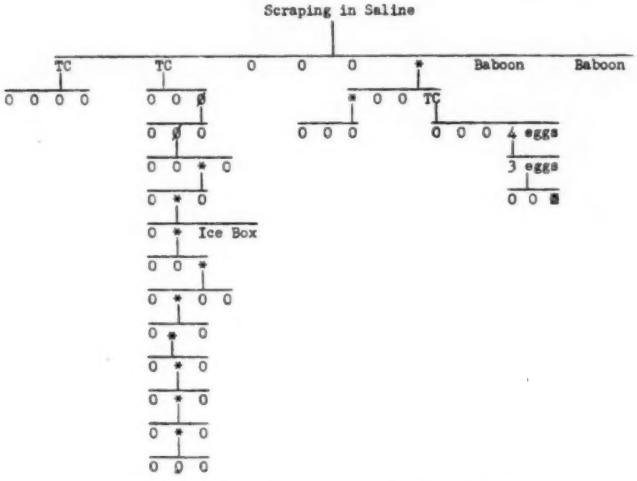

Chart 6.—Passage of material from case 3-P.

developed from this material, while in the baboons which had previously been inoculated with mouse brain material follicular conjunctivitis failed to develop.

The potency of the virus was maintained by passage in mouse brain, and inoculation was made of mouse brain material into the chorioallantoic membrane of developing hens' eggs and into the yolk sac. The agent grew readily in these mediums and could be transferred from the eggs back into the mice without difficulty. There were no specific lesions on the chorioallantoic membrane, the entire membrane being covered with a fine exudate. In all instances the embryo was dead after five days.

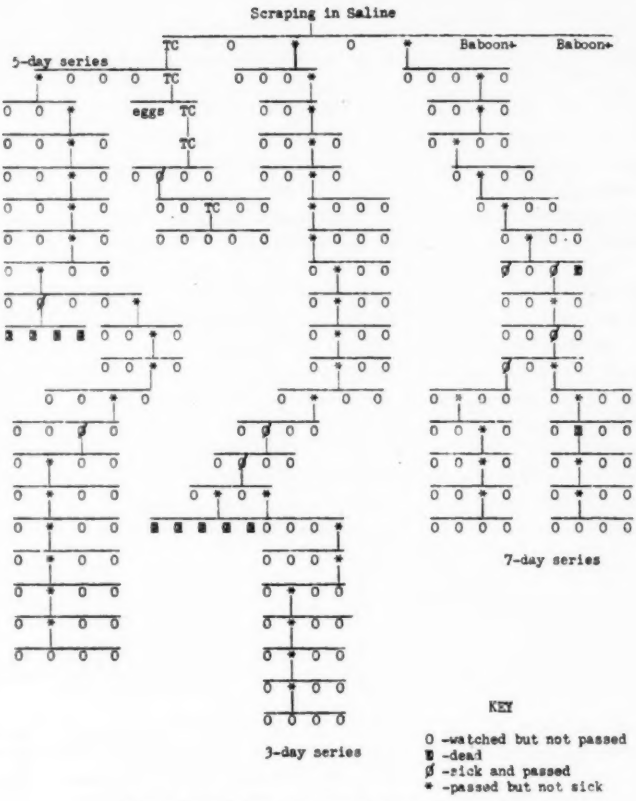

Chart 7.—Passage of material from case 2-AB.

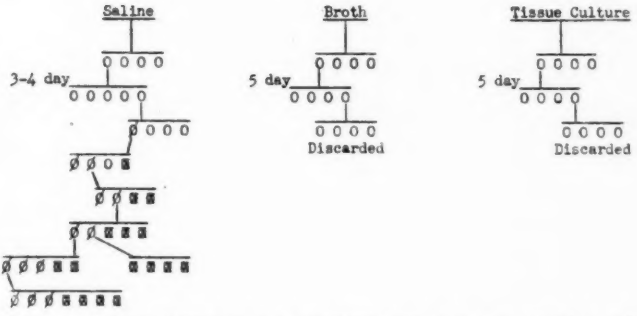

Chart 8.—Passage through mice of scrapings from baby's eye placed in saline solution and in broth and cultured. A titer of 1 : 100 was reached. The virus maintained potency up to 10^{-5} solution.

NEUTRALIZATION TESTS

Since it was possible that a known virus had accidentally been recovered, cross neutralization with virus immune serums was carried out. Antiherpes serum was mixed with the agent and inoculated on the chorioallantoic membrane. The herpes virus gives rise to a typical lesion on the chorioallantoic membrane of the developing hen's egg. When the virus is mixed with antiserum, these typical lesions do not develop. There was no evidence of neutralization with antiherpes serum to the virus of inclusion blennorrhea (table 2).

The possibility of infection with Theiler's virus was considered, since this virus is often present in mice and can be brought out by inoculation of sterile broth into the mouse brain. Although the mice used for experimental purposes were known to be free of this infection, Theiler immune serum was obtained in an attempt to neutralize our agent. The Theiler immune serum neutralized Theiler's virus up to $10,^{-2}$ but with our agent neutralization with Theiler's immune serum could not be obtained. The potency of the Theiler virus which was

TABLE 2.—*Inclusion Blennorrhea Virus with Antiserums for Three Viruses*

Theiler	Negative; no protection
Lymphocytic choriomeningitis	Negative; no protection
Herpes simplex	Negative; no protection

used for experimental purposes was relatively low and could not be increased beyond $10.^{-4}$ The agent was definitely not Theiler's virus.

Since the virus of lymphocytic choriomeningitis may have been a contaminant, an immune serum was made which prevented infection in the mouse brain with this virus. However, this immune serum did not protect the mice against our agent. It was thought, therefore, that the agent obtained was not the virus of lymphocytic choriomeningitis.

The original material was obtained from an infant, and it was not possible to obtain blood serum from the patient until a year and a half after the child had had the infection. In spite of this length of time, some indication of neutralization of the virus was obtained. Controls brought down mice in dilutions up to 10^{-7} and, when mixed with the baby's serum brought down mice in dilutions up to 10^{-5}. This would seem to indicate that the baby's serum had a trace of antibodies. Rabbits were immunized to the virus by intravenous injection of a small amount of live virus. After a period of six weeks, their blood contained neutralizing substances which would completely neutralize the virus. This substance was mixed with known viruses but showed no neutralizing power (table 3).

Serum was obtained from an adult with inclusion blennorrhea during the time that he had the infection. There was no evidence of neutralization of the agent. This fact, however, does not rule out the possibility that I may have been dealing with a virus-like inclusion blennorrhea, for it is known that in the case of the virus isolated from epidemic keratoconjunctivitis from two to three months is required for demonstrable immune bodies to be present in the blood serum. The known viruses that occur in mice are relatively small, usually in the neighborhood of 50 millimicrons. The virus of inclusion blennorrhea is considered to be more than 250 millimicrons; therefore, it would seem that filtration experiments should have given a lead as to the type of agent being dealt with. The virus of inclusion blennorrhea was difficult to filter through any of the candle type filters. It went through the Seitz filter without difficulty and maintained its potency. A series of Elford colloidin membranes were made. These were tested

TABLE 3.—*Blood of Rabbits Immunized to Inclusion Blennorrhea Virus Against Following Viruses*

	Inclusion Blennorrhea 10,000, Neutralizing Dose
Theiler	0
Vaccinia	0
Lymphocytic choriomeningitis	0
Lymphogranuloma venereum	0
Herpes simplex	0

by the usual method, and membranes were obtained with an average pore size of 500 to 50 millimicrons.

FILTRATION EXPERIMENTS

The filtration experiments with the gradocoll filter (a graded colloidin membrane with an average pore of diameter of 0.6 micron) were somewhat disappointing because the virus passed filters with an average pore size of from 250 to 500 millimicrons and was retained by filters below 250 millimicrons. Therefore, we assumed that the virus measured between 100 and 200 millimicrons and was at the edge of visibility with the microscope. The agent passed through the Berkefeld V filter but did not pass the Berkefeld W filter. The virus also passed the Chamberland L5 filter as well as the Seitz filter (tables 4 and 5).

STAINING EXPERIMENTS

Numerous smears, sections and touch preparations were made from the brain, lungs, nasal cavity, spleen, liver, peritoneum and blood. These were stained by the Giemsa method and with Victoria blue, iodine, aqueous methylene blue, copper sulfate, methylrosaniline U.S.P.

and phosphotungstic acid, as well as for acid-fast bacilli. Many of these stains were used in the hope that the stain would be absorbed by the virus, thereby increasing its size enough to be visible with the microscope. No definite virus could be demonstrated, although in both sections and smears bodies were seen that appeared to be elementary bodies, particularly in the phosphotungstic acid preparations. With this stain it requires considerable judgment on the part of the observer to distinguish between cell granules and elementary bodies. The virus may have been visible, but, because of the confusion with the numerous normal cell granules that are stained by several of the methods used, it was thought advisable to conclude that the virus was

TABLE 4.—*Ultrafiltration of Virus from Tissue Culture—Original Potency 10^{-2}*

Average Pore Size of Membrane, Millimicrons	Effect on Mice Dead : Inoculated
800-860	4:4
500-600	4:4
300-400	4:4
250-300	3:4
200-250	1:4
175-200	1:4
150-175	0:4

TABLE 5.—*Filtration Through Other Filters*

Average Pore Size of Membrane, Millimicrons	Effect on Mice Dead : Inoculated
Seitz	4:4
Chamberland 5	4:4
Berkefeld V	4:4
Berkefeld W	0:4

not demonstrated in stained preparations. There is no doubt that the virus obtained was in no way like the virus of inclusion blennorrhea as it occurs in the human conjunctiva. The elementary bodies and initial bodies are easily seen and are not confused with normal cell granules. The same is true for touch preparations made from mouse brain inoculated with lymphogranuloma venereum. The elementary bodies and initial bodies are easily defined from normal cell granules. The only conclusion that can be reached from the stained preparations is that the agent was not the virus of inclusion blennorrhea, but another virus which could not be identified.

Another means of checking the agent obtained to determine whether it was the virus of inclusion blennorrhea was its sensitivity to sulfonamide drugs. The standard procedure used was to feed sulfanilamide

and sulfadiazine to mice for three days prior to inoculation. The mice were therefore fed sulfonamide drugs in their food, according to the procedure used by Marshall.[7]

Serial dilutions were then given intracerebrally in the mice. There was no appreciable protection against the virus with either sulfanilamide or sulfadiazine, though the incubation period, which was normally three to four days, was extended to seven to ten days after the use of either of the drugs. However, mice died in the same numbers as in the control series.

Since we had obtained an overwhelming infection in mice that caused death within a week, we thought that the spleen, liver or lungs of the mice might give us a lead. The spleens and livers removed from the

TABLE 6.—*Distribution of Inclusion Blennorrhea Virus in Mice*

Route of Injection	Brain	Liver	Spleen	Lungs	Blood
Intracerebral	10^{-5}	10^{-6}	10^{-4}	Negative	10^{-3}
Intraperitoneal	10^{-4}	10^{-4}	10^{-3}	Negative	10^{-3}
Intravenous	10^{-6}	10^{-5}	10^{-4}	Negative	10^{-2}
Intranasal	Negative	Negative	Negative	Negative	Negative
Feeding by mouth	10^{-3}	10^{-3}	10^{-2}	Negative	Negative

TABLE 7.—*Pathogenicity for Other Animals*

	Cornea	Conjunctiva	Intracerebral	Intraperitoneal
Rabbit	Negative	Negative	10^{-3} (2 of 4 dead)	Negative
Guinea pig	Negative	Negative	Doubtful (1 of 5 dead)	Negative
Monkey	Negative	Doubtful	10^{-3} (1 of 2 dead)	Negative
Baboon	Negative	Follicular	10^{-3} Possible	Negative

mice were infectious on intracerebral inoculation of other mice. Smears of the liver and spleen failed to demonstrate any evidence of the virus. The lungs were noninfectious. Blood removed from the hearts of mice which died of the virus was also noninfectious when injected intracerebrally in other mice (table 6).

The virus was only moderately pathogenic when injected intracerebrally in rabbits and guinea pigs; however, the incubation period in both rabbits and guinea pigs was somewhat prolonged. The rabbits, however, formed antibodies to the virus if they survived. Rabbits were given a suspension of mouse brain and virus intravenously, and there developed a high degree of protective substances in their blood when it was mixed with the virus and injected intracerebrally in mice (table 7).

7. Marshall, E. K., Jr.: Physiol. Rev. **19**:240 (April) 1939.

The virus was attenuated if kept in a water bath at 60 C. for one hour. It killed 2 to 6 mice when injected with dilutions of $10.^{-1}$ Control mice in this series were all dead. The virus was apparently killed at 70 C. for one hour, for there were no deaths in 6 mice when the virus was injected in the same dilutions. The virus was also killed if heated at 60 C. for two hours.

The virus kept in the ice box remained active for two months, and it maintained its activity for three weeks in 50 per cent glycerin.

Since the virus could be grown well in tissue culture and remained infectious, I tested its growth in a tissue culture mixture which contained no living cells. The tissue culture was made of serum ultrafiltrate and balanced saline solution with finely divided embryonic mouse brain. With this culture the virus grew and increased in potency. If the embryonic mouse brain was omitted from the tissue culture, leaving only balanced saline solution and serum ultrafiltrate, the virus quickly died and became noninfectious.

The virus maintained its potency when kept frozen at — 60 C. It also maintained its potency for a period of six months after being completely dried in the lyophil apparatus.

After the virus was established, it could be passed intracerebrally, intravenously or intraperitoneally but could not be passed to mice by the intranasal or the oral route. Occasionally mice came down when they were fed the virus by mouth; however, this was not a particularly good method of inoculation.

All mice were susceptible regardless of size and age, and we were unable to develop an immune strain of mice by repeated inoculations of small amounts of the virus in high dilutions. Heavy suspensions of the virus were inoculated on the cornea of rabbits but produced no effect.

Attempts at digestion of the virus with pneumococcus enzyme and pepsin had little or no effect on the potency of the virus.

ATTEMPTS TO REPRODUCE THE DISEASE

Mouse brain material used in serial passage in mice was suspended in isotonic sodium chloride solution U.S.P. and inoculated on the conjunctiva of the baboon. Several drops of the infected material were rubbed onto the conjunctival sac of the baboon with a sterile cotton swab. The conjunctiva was watched for the development of conjunctivitis. With one of the agents, conjunctivitis was repeatedly obtained in baboons. The baboon would recover from the conjunctivitis in from two to six weeks. While the baboon had conjunctivitis, the tarsus of the upper lid and the retrotarsal fold of the lower and upper lids were covered with large follicles. This was associated with a slightly purulent discharge. Occasionally a small amount of edema was present in the upper lid. Epithelial scrapings from the conjunctiva repeatedly

failed to show inclusion bodies. After a period of approximately three months, these baboons were again inoculated with material obtained directly from babies with inclusion blennorrhea. Conjunctivitis did not develop in these animals, whereas in baboons which had previously been inoculated with inclusion blennorrhea virus from a baby or had never been inoculated with any virus inclusion blennorrhea developed. The baboons inoculated with inclusion blennorrhea virus 5 were entirely immune to further inoculation with inclusion blennorrhea from patients. There is no doubt that the virus which was so potent in mice gave rise to conjunctivitis in the baboon. The conjunctivitis, however, was not typical experimental blennorrhea. The conjunctivitis produced was a follicular type, similar to the spontaneous follicular conjunctivitis that sometimes occurs in baboons. Trauma to the lids may have produced some of the conjunctivitis, but this should have disappeared in a short time.

From past experience, it is known that the baboon does not maintain an immunity to inclusion blennorrhea after it has recovered from the disease. If material from the eye of a baby or an adult with inclusion blennorrhea is inoculated on the conjunctiva of a baboon, the result is a moderately severe follicular conjunctivitis, which lasts from one to two months. After the attack the baboon's eye can again be inoculated with material from an eye with inclusion blennorrhea and conjunctivitis is again produced, entirely similar to the first. It is doubtful, then, whether any immunity is developed by inoculation with material from inclusion blennorrhea.

Since the baboons were inoculated with a potent virus and exhibited a follicular conjunctivitis but an experimental inclusion blennorrhea failed to develop when they were inoculated with inclusion blennorrhea, the results can be explained by the so-called interference phenomenon, in which one virus will produce antibodies which are reasonably nonspecific and give some degree of protection against other viruses. This is especially true of the interference between herpes and vaccinia, since the inoculation with vaccinia will interfere with the development of herpes in the rabbit.

The experiment was repeated on 8 different eyes, and all the baboons showed an immunity to inclusion blennorrhea after having first been inoculated with the virus.

GENERAL COMMENT

The viruses of psittacosis, lymphogranuloma, trachoma and inclusion blennorrhea are morphologically similar. The viruses of psittacosis and lymphogranuloma grow well in an endothelial type of tissue, while the viruses of trachoma and inclusion blennorrhea seem to require

conjunctival epithelium in order to reproduce. The viruses of lymphogranuloma and psittacosis have both been adapted to the mouse brain, though often repeated passages of lymphogranuloma material are required finally to produce adaptation of the virus to the mouse brain. Once it is adapted, however, it grows well and can be studied easily. When the virus of lymphogranuloma is grown in mouse brain, smears of the brain usually reveal large numbers of elementary bodies. It would seem that if the virus of inclusion blennorrhea could be grown in the mouse brain it would likewise show large numbers of inclusion and elementary bodies on smears of mouse brain; however, repeated smears of virus obtained from the mice inoculated with inclusion blennorrhea did not demonstrate elementary or inclusion bodies. It was therefore assumed that the virus was changed so completely that it would not stain by the Giemsa method. On filtration experiments with the virus of inclusion blennorrhea with gradocoll filters, the virus should have been visible in the microscope, and the infectivity for the mice was so high that there should have been quantities of virus material on the stained smears. Other stains were used to identify the material, and with the phosphotungstic acid stain bodies were observed which simulated elementary bodies. The phosphotungstic acid stain, however, was so confusing in smear preparations that it was impossible to tell the elementary bodies from the cell granules.

CONCLUSION

It can be assumed that a new, unknown virus was isolated; however, it may represent a variant of the virus of inclusion blennorrhea. The psittacosis group of viruses, in their natural form, stain like bacteria. On the whole, their pathogenic activity is more like a moderately virulent bacterium than like a virus. Their requirements for multiplication are, however, those of a typical virus. Burnet[8] has shown that mutation occurs in virus diseases. This is considered true of the influenza virus, of which types A, B and C are examples.

In the manner in which the virus of inclusion blennorrhea was handled in passing through the mouse brain, it is quite possible that a mutation of the inclusion blennorrhea virus may have occurred, transforming an atypical virus into a typical one. This could explain all the seemingly peculiar experimental data presented here.

If one can assume that the unknown virus which I present is a variant of the virus of inclusion blennorrhea, one can say that it has been transformed into a true virus. This virus, then, could give rise to a

8. Burnet, F. M.: Virus as Organism: Evolutionary and Ecological Aspects of Some Human Virus Diseases (the Edward K. Dunham Lectures for the Promotion of the Medical Sciences), Harvard Monographs in Medicine and Public Health, no. 8, Cambridge, Mass., Harvard University Press, 1945.

follicular conjunctivitis in baboons in which there might be immunity to further inoculation with the virus of inclusion blennorrhea from a patient. The patient's serum carried antibodies to the virus about a year after the original infection, even though they were low in potency. This assumption would also explain the large filtration size of the virus, the difficulty in staining and the development of antibodies in rabbits and baboons. If viruses are considered a mutation from bacteria by loss of their ability to synthesize artificial mediums, it appears highly probable that a mutation of an atypical virus could be brought about. Beadle [9] and his collaborators, working on a mold, Neurospora, which grows on almost anything, found that by treating this mold with roentgen radiation variants were produced which required a complex medium for growth. These investigators produced over two hundred such variants. Although there is considerable difference between this mold and the viruses of the psittacosis group, one may consider that all four diseases may represent variants of the original virus. Since this group is closely related in some respects to bacteria, e. g., in staining properties and in sensitivity to the sulfonamide drugs, and in other respects to viruses, variants could have occurred.

It is therefore concluded that the virus of inclusion blennorrhea as it occurs in the human eye was not grown, but that a variant which was a true virus was produced from the atypical virus of inclusion blennorrhea.

9. Beadle, G. W., and Tatum, E. L.: Proc. Nat. Acad. Sc **27**:499 (Nov.) 1941.

USE OF PHENYLEPHRINE HYDROCHLORIDE (NEO-SYNEPHRINE HYDROCHLORIDE®) IN OPHTHALMOLOGY

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THE FIRST studies on the ocular use of phenylephrine hydrochloride (neo-synephrine hydrochloride®) were begun in 1933 and reported in 1936.[1] Since then, extensive clinical experiences with this drug have accumulated with additional observations. The object of this article is to review these data, bringing them up to date.

Phenylephrine hydrochloride (laevo-α-hydroxy-β-methylamino-3-hydroxyethylbenzene hydrochloride) is the salt of the laevo isomer of a synthetically prepared derivative of phenylethylamine. It is a white, crystalline, nonhygroscopic compound, readily soluble in water and alcohol. It is relatively stable. The melting point ranges from 138 to 142 C.

Pharmacologically, phenylephrine belongs to the group of compounds possessing sympathomimetic activity. It is an active vasopressor agent when given either orally or parenterally. As a vasoconstrictor, it has the desirable quality of rarely causing any compensatory dilatation. Phenylephrine relaxes the sphincter muscle of the iris and strongly contracts the radial fibers. This characteristic, together with its pronounced decongestive action, makes it valuable to the ophthalmologist. Occasionaly light cycloplegia is observed after topical application of the 10 per cent preparations. The lowering of intraocular pressure from the use of this compound is not constant, and in this role it is like epinephrine. Isolated and in situ studies of the effects of sympathomimetic compounds on the iris are well known. Conclusive studies on the epinephrine-like compounds and their precise effects on the ciliary ring are not known to have been reported. (Subconjunctival injections of phenylephrine do not enhance its effectiveness.)

1. (*a*) Heath, P.: Neosynephrine Hydrochloride: Some Uses and Effects in Ophthalmology, Arch. Ophth. **16**:839 (Nov.) 1936. (*b*) Post, W. L.: Neosynephrine, Am. J. Ophth. **20**:170 (Feb.) 1937. (*c*) Heath, P., and Geiter, C. W.: Some Physiologic and Pharmacologic Reactions of Isolated Iris Muscles, Arch. Ophth. **21**:35 (Jan.) 1939.

Primarily, solutions of phenylephrine hydrochloride in the 2.5 and 10 per cent solutions contained ascorbic acid. This substance is a powerful reducing agent; and, while it was a great aid in preventing oxidation of the phenylephrine, after a short time in solution it produced an amber discoloration. However, the chief undesirability of ascorbic acid was due to its lowering of the p_H, causing stinging, and also preliminary congestion, on topical application. The new solutions do not contain ascorbic acid but do contain a buffering agent, which stabilizes the p_H and greatly reduces the irritation.

Solutions for ophthalmic preparations should possess certain specific characteristics when possible. The ideal range of the p_H is from 7.0 to 7.6, although solutions with a lower p_H do not necessarily cause stinging. Irritation may be of benefit if vasodilation goes with it, and is in itself beneficial, or harmful, if dilution from tearing results. Ophthalmic solutions should be adjusted so that their isotonicity is within the range of a 1.0 to 1.4 per cent solution of sodium chloride, the higher percentage being equivalent in isotonicity to that of tears (1.32 to 1.427). The isotonicity is usually determined by the freezing point. While the optimum gravity for ophthalmic solutions is suggested as 1.004 to 1.005, it is not clearly understood just what part this factor plays. The range apparently is wide, since our experiments have shown considerable latitude. Some ophthalmic solutions should contain wetting agents. Primarily, the basic medication should be capable of penetrating the cornea and be compatible with the wetting agent; otherwise, the addition of this agent is of little value. Local irritation from a medical preparation is of decided secondary importance to achieving effective concentration of the medicament at the suitable point of action. If possible, the vehicle for the ophthalmic drug should be self sterilizing.

Since one of us (P. H.) [2] introduced one of the first low tension ophthalmic preparations in the form of an oil-in-water emulsion, many wetting agents have been suggested and used. Bellows and Chinn; Gifford, and O'Brien and Swan have demonstrated that the use of wetting agents definitely enhances the penetrability of many useful ophthalmic drugs. However, even with the recent advances in pharmaceutic chemistry, it is impossible in many instances to prepare certain drugs within the range of the previously mentioned specifications for an ideal ophthalmic preparation. This is true because the stability of the different commonly used drugs varies according to the p_H of the solution, as Gifford has pointed out. Some high percentage solutions

2. Heath, P.: Use of Emulsions in Ophthalmology, Am. J. Ophth. **22**:904 (Aug.) 1939.

have a greater tendency to produce undesirable irritation in spite of their other component pharmaceutic perfections. For example, 1 Gm. of phenylephrine hydrochloride is equivalent in isotonic properties to 0.28 Gm. of sodium chloride.[3] The 2.5 per cent solution is approximately isotonic (equivalent to 1.2 per cent sodium chloride solution) with the preservatives, wetting agent (0.001 per cent aerosol OT 100 per cent, or sodium dioctylsulfosuccinate) and buffer added. With 10 per cent it is impossible to make an isotonic solution, because in this concentration it would be equivalent to at least a 2.8 per cent solution of sodium chloride. With the other necessary salts added, its isotonicity is approximately equivalent to that of 3.3 per cent sodium chloride solution, which causes some pain unless a topical anesthetic is used first. In contrast to this, the 10 per cent emulsion is not nearly so irritating, a characteristic which is due in part to the emollient effect of the oil content.

CLINICAL USES OF PHENYLEPHRINE HYDROCHLORIDE

1. As a decongestive agent, for use in mild conjunctivitis, the prescription may contain 0.0125 per cent phenylephrine hydrochloride in association with other drugs. It should not be used indefinitely. To produce a substantial decongestion of the globe, one may use a 10 per cent emulsion or a 10 per cent solution, instilled after the use of a topical anesthetic. After application of the emulsion, dry particles of acacia (part of the emulsion base) may be observed on the lid margins. These are readily removed with moistened cotton.

2. Phenylephrine hydrochloride may be used as a mydriatic for the following purposes: (*a*) In examination of the fundus. The best prescription for this use is a 2.5 per cent solution dropped once or twice in the eyes; for more rapid dilation a drop is applied every five minutes three or four times.

(*b*) In breaking adhesions of the iris to the lens (sometimes to the cornea). For this purpose, it is best to apply the 10 per cent emulsion to the upper portion of the cornea, after preliminary instillation of 1 drop of a topical anesthetic and an interval of two minutes. Sometimes the use of atropine contracts the pupil partially after the use of the phenylephrine. The interval of dilatation following instillation of the stronger solution varies from two to six hours.

(*c*) In refraction, especially in cases of presbyopia and myopia. This enables one to obtain an objective measurement with the shadow

3. Welles, J.: Calculating Isotonic Solutions, J. Am. Pharm. A. **5**:99 (April) 1944.

test, as well as to examine the fundus by ophthalmoscopy. Higher errors of both sphere and cylinder, overlooked by subjective testing, may be derived through objective examination. A 2.5 to 5 per cent solution is used.

(*d*) In cycloplegia. When the iris is resistant to dilation with the usual cycloplegic, although one may have paralysis of the ciliary body, the addition of phenylephrine will often produce a wider dilatation of the pupil.

(*e*) In overcoming extreme miosis in glaucoma. It may be used with miotics. Its decongestive effect is valuable, especially in cases of glaucoma of the shallow anterior chamber type (Sugar[4]); and its prolongation of the effect of the miotic is also useful. Furthermore, it reduces the difficulties experienced by the patient because of the small field, due to the extremely narrowed pupil, and still permits, and often supports, the effect of the miotic in lowering the intraocular pressure. Post[1b] reported using phenylephrine with physostigmine. If the increased intraocular pressure is based on a mechanical blockage of the angle, it is important to avoid a solution of phenylephrine of sufficient concentration to bring about this hazard. Experience from trial with weak solutions, from 0.25 to 1.0 per cent and upward, will give the desired information on the action of the drug.

(*f*) In beginning intraocular operation when one wishes to have the benefit of a widely dilated pupil at the time of operation and then to have the pupil contract shortly thereafter. It is useful in cases in which a needling is to be performed for secondary cataract operation and in cataract operations in general, and even in cases of increased intraocular pressure or borderline pressure. The dilatation facilitates the removal of the lens, and postoperative contraction of the pupil may be induced by miotics. A 2.5 per cent solution, to be repeated, or a 5 per cent solution given once, is the best prescription.

(*g*) In provocative testing for glaucoma induced by dilated pupils. A rapid miosis may be readily induced with the usual miotics.

(*h*) As a supplement to a mydriatic when there is sensitivity to the mydriatic used.

3. This compound is of great value in infiltration anesthesia, both for major and minor surgery, for the following reasons: (*a*) The drug acts as a decongestive; (*b*) prolonged action of the infiltration anesthesia is maintained; (*c*) there is slower absorption; (*d*) the drug is an antispasmodic; (*e*) there are few or no side reactions. The best prepa-

4. Sugar, H. S.: Acute Glaucoma: A Follow-Up Study, Am. J. Ophth. **30**:451 (April) 1947.

ration for this purpose is a 1 per cent sterile solution. This is used in a proportion of 0.3 to 0.5 cc. of 1 per cent sterile solution to 10 cc. of anesthetic solution (1:3,333 to 1:2,000).

4. Its use with application of cold in the reduction of edema and congestion in the allergic form of acute conjunctivitis has been reported by Koch.[5]

5. Phenylephrine has been combined with sulfathiazole.[6] This salt in an 0.6 per cent solution is equivalent in vasoconstrictor action to the 0.25 per cent of the phenylephrine hydrochloride. It has a limited use in ophthalmology—the 0.6 per cent solution has bacteriostatic properties useful in cases of obstinate blepharitis.[7]

6. Phenylephrine hydrochloride, 0.25 per cent, has also been combined with tetracaine (pontocaine®) hydrochloride, 0.5 per cent, for ocular and nasal application to overcome pain and blepharospasm and to permit further treatment after exposure to irritating gases and "flash" burns in industrial medicine.

7. The hemodynamic properties of phenylephrine hydrochloride have been used clinically by Johnson [8] in cases of shock. The dose is 5.0 to 10.0 mg. given subcutaneously or 3 mg. given intravenously.

COMMENT

Rapid absorption of substantial amounts of phenylephrine causes marked and hazardous increase of the blood pressure. Systemic absorption through the anterior segment of the eye is slow and limited in degree. To investigate this, a study was made on 60 clinic patients and 60 private patients. This study included the measurements of the blood pressure and the intraocular pressure before instillation of phenylephrine into the eyes. These two measurements were then made one hour after the instillation of the drops. A variety of ophthalmic and general disease states were represented in each group of subjects, among them incipient glaucoma, aphakia, cataract, hypertension, renal disease, blood dyscrasias and diabetes. The blood pressure readings after use of phenylephrine were unaltered in about 40 per cent of the cases, lowered slightly in about 58 per cent and slightly increased in

5. Koch, F. L. P.: Ophthalmological Expressions of Allergy, Eye, Ear, Nose & Throat Monthly **23**:483 (Dec.) 1944.

6. Geiter, C. W.; Lands, A. M., and Lewis, J. R.: A Study of a New Salt of Neosynephrine, J. Am. Pharm. A. (Scient. Ed.) **33**:359 (Nov.) 1944.

7. Heath, P.: Chemotherapy in Ophthalmology, J. A. M. A. **124**:152 (Jan. 15) 1944.

8. Johnson, C. A.: Study of Neo-Synephrine Hydrochloride in Treatment of Acute Shock from Trauma or Hemorrhage, Surg., Gynec. & Obst. **63**:35 (July) 1936.

2 per cent. A variation of ± 4 mm. was designated as "no change" and a drop or rise, on the basis of 5 mm. or over. From this investigation it was concluded that no significant changes in either blood pressure or intraocular pressure were produced, this conclusion being subject to one qualification, namely, that in cases with narrowed angle, blockage from iris tissue can occur as the pupil is dilated, thus causing increased intraocular pressure.

We have never noted or had reported any harmful effects on the ocular tissues or the blood vessels from the use of this substance. Neither sensitivity nor delayed healing has been reported. Phenylephrine hydrochloride has a wide range of uses and has firmly established its importance in ophthalmology as a valuable therapeutic and diagnostic substance.

Massachusetts Eye and Ear Infirmary, Boston (Dr. Heath).
North Kansas City (Route 4), Mo. (Dr. Geiter).

JUXTAPAPILLARY HEMANGIOENDOTHELIOMA OF THE RETINA

Report of a Case

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THE OCCURRENCE of hemangioendothelioma of the retina, or von Hippel's angiomatosis retinae, is frequent enough to be hardly worthy of special comment. The case which is presented, however, is sufficiently interesting and unusual to be brought to the attention of ophthalmologists.

REPORT OF CASE

H.S., a medical officer aged 40, white, was admitted to Dibble General Hospital on March 27, 1945, for investigation of blurred vision in the right eye of ten months' duration. This symptom was first observed when the patient noted that he could not focus with his right eye when using a pair of field glasses. His records indicated that in June 1943, prior to his departure overseas, vision was 20/25 in his right eye and 20/20 in his left eye with a mild correction for myopia. The patient showed no immediate concern over his newly discovered blurred vision in the right eye, but three months later, in October 1944, he visited the eye clinic of an overseas general hospital, where examination indicated the probability of "an exudative hemorrhagic lesion of the optic nerve." Visual acuity in the affected eye was 20/200, with correction, and no further study was conducted at that time. In February 1945 the patient was examined in the eye clinic of another overseas general hospital, where the possibility of a tuberculoma of the optic nerve or of retinochoroiditis juxtapapillaris was suggested. The patient was then returned to the United States on the basis of an ordinary leave, to visit his sick mother. On arriving in this country, he reported to a dispensary at Fort Mason, San Francisco, where an ophthalmologic examination disclosed what was thought to be a tumor of the optic nerve. The patient was then transferred to Dibble General Hospital for continued observation and treatment.

On his admission to this hospital, a complete physical examination indicated that the pathologic process was limited to the right eye. The past medical and family histories were essentially noncontributory.

The ophthalmologic examination revealed vision of 8/400, correctible to 20/300 with a —1.25 D. sphere in the right eye and 20/50, correctible to 20/15 with a —1.25 D. sphere in the left eye. No test letters on a Jaeger chart were visible at the near point with the right eye. Ability to read Jaeger test type 1 was recorded for the left eye.

External examination of the right eye showed full ocular rotations, normal intraocular tension on palpation and dilatation of the pupil, due to a mydriatic drug.

Submitted for publication with the cooperation of the Army Institute of Pathology; Colonel Raymond O. Dart, Medical Corps, United States Army, Director.

There was no exophthalmos, readings with the Hertel exophthalmometer indicating 16 mm. for each eye. The left eye appeared normal. Examination with the slit lamp revealed no abnormality in the anterior segment of either eye.

Ophthalmoscopic examination of the right eye was reported as follows (fig. 1): The media were clear. A large, round, orange mass was seen to arise from the temporal aspect of the disk and extend laterally toward the macula. The diameter of the lesion was estimated to be slightly more than 1 disk diameter, and its elevation, 2.5 D. Its surface presented a mottled effect, and moderate vascularity was apparent. The border showed a condensation of pigment. A portion of the tumor appeared to surround the superior temporal vein (not shown in the artist's conception of the tumor), and a number of large blood vessels were seen in the tumor; these vessels extended from the retinal circulation. The macular region appeared

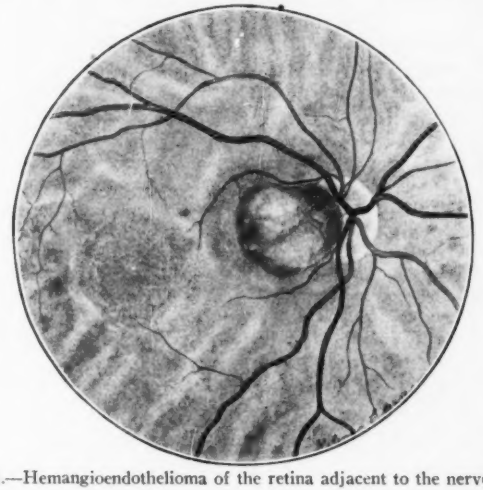

Fig. 1.—Hemangioendothelioma of the retina adjacent to the nerve head.

somewhat elevated, the result of edema. The rest of the fundus appeared normal. The left eye was normal.

Examination of the central visual field was made shortly after the patient's admission to the hospital; unfortunately, the record of this examination could not be obtained for illustration. The examination revealed enlargement of the blind-spot and a central scotoma to red, which measured 5 degrees, was noted.

Roentgenographic studies of the skull and optic foramens were conducted, revealing a normal status. Blood studies and urinalysis also gave normal results. The patient was seen in consultation by Dr. Frederick C. Cordes, civilian consultant in ophthalmology of the Ninth Service Command, who corroborated the report. Dr. Cordes suggested the diagnostic possibility of perithelioma or of neuroepithelioma of the optic nerve. The patient's course in the hospital prior to enucleation was remarkable only for the improvement in visual acuity in the affected eye to 20/30, with correction, as determined on May 15; and examination of the central visual field at this time revealed a large pericentral scotoma which practically encircled the fixation point.

Ophthalmoscopic study at this time suggested increase in the area of the tumor, although there was no increase in its elevation. It was also believed that the surrounding retinal edema had diminished somewhat, a change which probably explained the improvement in visual acuity and the disappearance of the central scotoma originally observed. In spite of definite improvement in visual acuity, it was felt that the patient presented a malignant tumor of the right optic nerve, and enucleation was recommended.

Operation was performed on May 22. At the time of enuclation 2 cc. of vitreous humor was aspirated through a scleral incision for use in a transplantation to another patient.[1] The eyeball was enucleated in the usual manner, and care was taken to obtain a long section of the optic nerve. The enucleated eye was replaced by a basket type acrylic implant, described by Cutler.[2]

Healing of the socket was uneventful, and a satisfactory acrylic prosthesis was ultimately fitted. The patient's general condition remained satisfactory throughout the period of observation, which continued until December 1945.

Pathologic Study of the Eye (Army Institute of Pathology; Director, Col. J. E. Ash, Medical Corps).—The following report, dated July 11, 1945, was submitted by the Institute (fig. 2):

"Gross Study: The specimen consisted of an eye measuring 25.5 by 24.5 mm. There was a sutured scar almost at the equator. The eye was opened in the horizontal plane. A small, opaque, elevated, granular lesion, about 2 mm. in diameter, arose from the cupped optic disk and encroached on the retina, almost to the swollen macula. There was a posterior synechia.

"Microscopic Study: The cornea was not remarkable. The angle of filtration was clear. There were posterior synechias with a partial ectropion uveae. The ciliary processes showed more hyalinization than usual for one of the patient's age. The choroid was not remarkable. Some round cell infiltration was present about the posterior episcleral vessels, with a margination of polymorphonuclear leukocytes. Most of the lens substance was absent. The retina was detached, and anteriorly there was a very small hemorrhage. Some serous exudate lay beneath the macula anteriorly, where the latter was cystic. Arising apparently in the nerve fiber layer at the margin of the disk was a small tumor, made up of round and spindle cells, some of the former with a generous amount of cytoplasm, which was usually vacuolated. The tumor was highly vascular; the vessels were thin walled. The tumor had invaded the retina as far as the external limiting membrane and had extended onto the temporal half of the disk. Clusters of cells lay among the nerve fibers just outside the cribriform plate. These did not have quite the neoplastic character of the cells of the tumor. They probably represented reactive gliosis. The tumor extended in the nerve fiber and ganglion cell layers into the edge of the macula. There were large cystic spaces in the inner nuclear and outer plexiform layers of the macula. The tumor is interpreted as a glioma of the retina of mixed cell type, including oligodendroglia with a few astrocytes. It is not considered malignant. It is felt that the neoplasm has been entirely removed. Gross section of the optic nerve showed no tumor."

Additional study of the tumor by the Army Institute of Pathology led to the revised diagnosis of von Hippel's hemangiogliomatosis.

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1. Cutler, N. L.: Transplantation of Human Vitreous, Arch. Ophth. **35**:615 (June) 1946.

2. Cutler, N. L.: A Basket Type Implant for Use After Enucleation, Arch. Ophth. **35**:71 (Feb.) 1946.

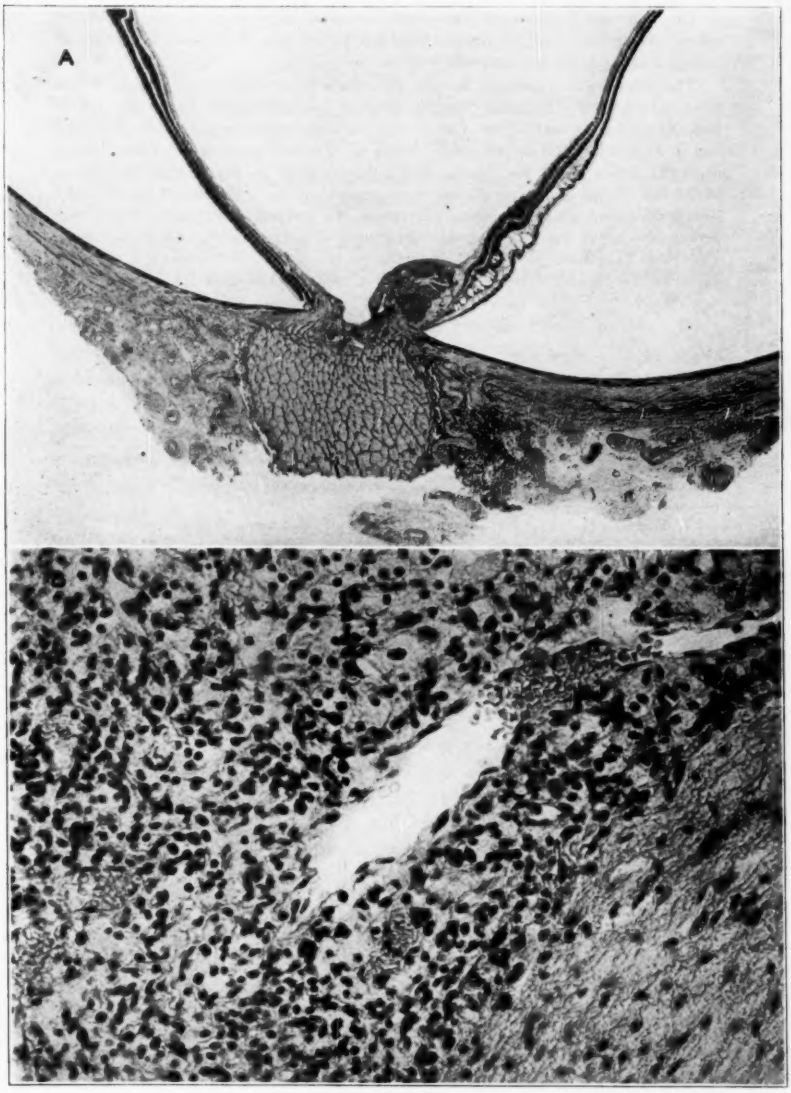

Fig. 2.—*A*, well circumscribed tumor, a hemangioendothelioma of the retina; × 11. Army Institute of Pathology, negative 103083.

B, high power view of the tumor in *A*, showing rich vascularity and formation of capillary elements; × 236. Army Institute of Pathology, negative 102957.

Dr. Algernon B. Reese, of New York, examined sections of the tumor and also voiced the opinion that the disease belonged to the von Hippel–Lindau group of lesions designated as angiomatosis retinae.

The tumor was examined by Dr. Frederick H. Verhoeff, of Boston, whose comment follows: "The cells resemble those of proliferating capillaries and appear to be derived from capillaries. I think there is little neuroglia in the tumor proper, and I should not think otherwise unless a stain for neuroglia showed many neuroglia fibrils within the tumor. Since the tumor is an angioma, it may belong to the von Hippel group, in spite of its unusual location. However, I cannot make such a diagnosis without evidence other than the histologic character of this particular tumor. It does not resemble the growth associated with tuberous sclerosis. The blood is stained poorly, a fact which makes it difficult to perceive the true nature of the tumor. I think the tumor is a hemangioendothelioma."

COMMENT

A case of von Hippel's angiomatosis retinae in an Army medical officer aged 40 is reported. The tumor was situated immediately adjacent to the optic nerve head, leading to the preoperative impression of a malignant tumor of the optic nerve. It is of further interest to note that a similar lesion has been seen in another military patient, as recently reported by Wilder.[3]

3. Wilder, H. C.: Intra-Ocular Tumors in Soldiers, World War II, Mil. Surgeon **99**:459 (Nov.) 1946.

SCLEROMALACIA PERFORANS

Report of a Case

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IN 1934 van der Hoeve[1] reported a new disease of the eye, which he called scleromalacia perforans. He concluded that the disease was a degenerative, rather than an infectious, process and that it usually accompanied rheumatoid arthritis. He accurately noted the early yellowish excrescences and the holes in the sclera which succeeded them, producing exposure of the uvea and the characteristic picture of the disease.

Occasional reports appeared after this, but they were so few that one must conclude that the disease is exceedingly rare. In 1938 Verhoeff and King[2] collected 14 cases from the literature; on the basis of an analysis of these cases, with 1 of their own, they gave the first pathologic report of the condition. In their summary, they stated, "Histologically, in their initial state the scleral nodules are essentially similar to the subcutaneous nodules of rheumatoid arthritis." Since 1938, 1 case has been reported by Eggers[3] and a few cases have been mentioned by discussants of other cases. The present case is therefore reported in order that another instance of a rare disease may be added to the scanty literature and that attention may be called to an associated degeneration—marginal dystrophy of the cornea.

According to Verhoeff and King,[2] the lesion starts as a small elevated, yellowish nodule, which consists of a small, central, sterile abscess, surrounded by several layers of epithelioid cells. Fragments of necrotic sclera can be seen, and plasma cells and fibroblasts are present in the scleral clefts, beyond the wall of epithelioid cells. Where the process is severe, the plasma cells undergo colloid degeneration,

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Read at a meeting of the New York Academy of Medicine, Section of Ophthalmology, Oct. 20, 1947.

From the Ophthalmological Service of Queens General Hospital; W. Guernsey Frey, M.D., Director.

1. van der Hoeve, J.: Scleromalacia Perforans, Arch. Ophth. **11**:111 (Jan.) 1934.

2. Verhoeff, F. H., and King, M. J.: Scleromalacia Perforans, Arch. Ophth. **20**:1013 (Dec.) 1938.

3. Eggers, H.: Necroscleritis Nodosa Associated with Chronic Arthritis, Arch. Ophth. **23**:501 (March) 1940.

and the underlying uvea degenerates. In a variable period, the contents of the abscess are extruded and an area of uvea is exposed. This area is usually covered by a thin layer of fibrous tissue. The conjunctiva may cover the defect, or only the borders of the defect. The pathologic changes are confined to the anterior portion of the sclera.

The disease characteristically occurs in the sixth, seventh and eighth decades of life. In the great majority of cases reported there was severe rheumatoid arthritis of long duration. The onset is usually insidious, with little or no pain and without visual disturbances. The scleral excrescence is accompanied with a localized area of scleral injection and superficially resembles episcleritis. In some cases the abscess is absorbed without sequestration of scleral tissue and no breakdown occurs. In such cases the diagnosis may not be made. In others, in a variable period (three to four weeks in this case) the nodule opens and discharges its content, leaving a small area of exposed uvea, which is the characteristic lesion. With the formation of similar foci about the original lesion, and their breakdown, the defects become coalescent, leaving large scleral holes.

A low grade iridocyclitis may complicate the disease at some stage of its progression. Both Eggers [3] and Kiehle [4] reported iritis in their cases. Van der Hoeve [1] reported atrophy of the iris in 1 of his cases and endophthalmitis in 1 of Rochat's cases. Eggers' case, which was of a fulminating character, ended with hemorrhages in the vitreous and sclerosing keratitis. Verhoeff and King [2] found no report of central corneal opacities in any case and noted mention of cataract in only 3 cases.

The disease may involve only one eye, or it may be bilateral. The duration is variable, and vision is not seriously affected by the scleral disease, but, as intraocular complications develop in most cases, the prognosis for vision is poor.

There is no known treatment of any value. Oast [5] reported a good result with ultraviolet irradiation in his case, but this patient did not have rheumatoid arthritis. Duke-Elder [6] mentioned placing a mucous membrane graft to cover the scleral hole. There is no report on the value of this procedure.

REPORT OF CASE

History.—On Jan. 16, 1947, E. K., a white woman aged 70, was admitted to the Queens General Hospital for treatment of mild pneumonitis, which resolved in a few days. The patient had been bedridden for the past two years because of rheumatoid arthritis involving most of the joints of the body. When the patient was 30 years of age, the disease began in the right shoulder and had gradually involved

4. Kiehle, F.: Scleromalacia, Am. J. Ophth. **20**:265 (June) 1937.
5. Oast, S. P.: Scleromalacia Perforans, Arch. Ophth. **17**:698 (April) 1937.
6. Duke-Elder, cited by Kiehle in discussion on Verhoeff and King.[2]

the knees, ankles, hands, wrists, elbows, hips and spine. She had received many types of therapy, including massive doses of vitamin D and gold salts, without appreciable benefit. About one year before her admission the patient began to have pain, burning and lacrimation of the eyes with gradual loss of vision.

Ocular Examination.—The eyes were kept closed; although the patient could open them voluntarily, she could not keep them open for more than a few seconds. Vision was limited to light perception in the right eye and consisted in counting fingers at 2 feet (60 cm.) in the left eye. Both corneas were clear, and the pupils were miotic and irregular. The pupils could not be dilated with atropine owing to the presence of dense posterior synechias. The lenses showed early cataractous changes, and the fundi could not be observed. Tension in each eye was very low, being below 10 mm. (Schiøtz). The lids were normal. The conjunctivas were diffusely reddened and thickened, and there was a scanty, dirty gray exudate in

Fig. 1.—Direct view of left eye, showing large scleral hole and exposed uvea above, with smaller hole below and developing area temporally.

the lower fornices. There was profuse lacrimation during the examination. In each eye, 4 mm. above the limbus, there were scleral holes, measuring 3 by 4 mm. In the right eye, on the nasal side of the limbus, there were two similar areas, measuring less than 1 mm. in diameter. The uvea could be readily seen lying under a thin layer of transparent fibrous tissue. The conjunctiva overlapped these areas slightly. There were deep grooves in both upper limbal areas, with a steep shelf on the corneal side and a sloping shelf on the scleral side.

Laboratory Studies.—Laboratory examinations did not reveal anything remarkable. The Wassermann reaction of the blood was negative. Chemical analysis of the blood showed urea nitrogen, 15 mg.; albumin, 4.3 Gm.; globulin, 2.1 Gm.; cholesterol, 175 mg.; cholesterol esters, 110 mg., and sugar, 125 mg. per hundred cubic centimeters. The red cell count was 3,770,000, with 10 Gm. of hemoglobin, and the white blood cell count was 10,900, with 90 per cent polymorphonuclear

leukocytes and 10 per cent lymphocytes. The urine was normal. Roentgenographic examination revealed partial demineralization of the entire skeleton. The joint spaces were narrowed, and their surfaces were eroded in the carpal, knee, hip and vertebral areas.

Subsequent Course of Illness.—The patient was given local instillations of penicillin (1 cc., equivalent to 2,500 units) every two hours; atropine and hot compresses were also used. In a few days there was considerable subjective improvement; the discharge disappeared, and the conjunctiva became paler. However, there was no change in the general appearance of the eyes. The pupils failed to dilate, and two weeks after her admission a small yellow-gray excrescence was noted in the sclera of the right eye. Three weeks later this had disappeared, leaving a small hole. These holes seemed to enlarge by a gradual necrosis of the scleral tissue. Occasionally excrescences appeared, but the greatest progression of the lesion seemed to be due to a gradual melting away of the sclera at the margin of a defect. On April 3, endophthalmitis appeared in the right eye; the cornea grad-

Fig. 2.—Somewhat lateral view, showing deep superior temporal furrow in corneal limbus. The white areas are due to defects in the photograph.

ually clouded, and light perception was lost. Two weeks later, while attempting to photograph this eye, I saw the marginal furrow in the cornea perforate and the uvea bulge through the large scleral defect above the limbus. The eye became painful and was enucleated. At the time of this report, the left eye has suffered reduction in vision to perception of light, and scleral holes almost ring the cornea. The cornea is opacifying, and it is likely that the eye will become painful in time and will require enucleation.

Pathologic Report (Dr. Alfred Angrist).—The specimen consisted of a globe, which was distorted and collapsed, with a large perforation at the limbus. The cornea presented an irregular epithelial cover, with partial loss of epithelium. The lens was absent. The iris was adherent to the cornea throughout. The retina and choroid had been detached in fixations. The sclera showed a large area of defect, with several similar smaller areas.

In microscopic section, the cornea showed necrosis of the lamellas in the substantia propria. Here the collagenous fibers were swollen and appeared homogeneous, with basophilic detritus and granularity. Adjacent to such areas, considerable infiltration with polymorphonuclear leukocytes was present, with proliferating fibroblastic tissue. This was prominent in the region of the perforation, where Descemet's membrane was folded. The corneal epithelium had grown downward into the region of the perforation. Some proliferating nodules of large fibroblastic cells were seen beneath Descemet's membrane. The adjacent conjunctiva showed nonspecific inflammation and congestion.

The sclera showed zones of central necrosis with granular debris, suggesting disruption of inflammatory cells; these zones were surrounded by fibroblasts and epithelioid cells, which had a tendency to radial arrangement. In such areas an occasional giant cell was seen. One such cell had a characteristic Langhans arrangement of the nuclei. The necrotic areas in the sclera surrounded by zones of epithelioid and round cells were more extensive than are usually the subcutaneous nodules found in rheumatoid arthritis.

The uvea showed inflammatory infiltration, especially in the iris and the ciliary body; the infiltrate was much less conspicuous posteriorly. Numerous hemorrhages were present in the retina, choroid and ciliary body. The retina was considerably disorganized and folded, with extensive destruction of the neuroepithelium. There was a notable reduction in the number of ganglion cells.

SUMMARY

A case of scleromalacia perforans is described and added to the scanty literature of this disease. The clinical appearance of the lesion and the pathologic features conformed closely to the description by Verhoeff and King. The disease accompanied chronic rheumatoid arthritis of long standing and, in the course of about twenty months, slowly progressed to involve most of the anterior portion of the sclera in a necrotizing process. The eyes have become blind as a result of an accompanying uveitis. An unusual feature of this case was an associated marginal necrosis of the cornea.

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CONGENITAL PTOSIS

A Classification of Two Hundred Cases

RAYNOLD N. BERKE, M.D.
HACKENSACK, N. J.

THE PURPOSE of this paper is to present a classification of congenital ptosis illustrating its diverse and complicated nature. Such a presentation is desirable because the operative results of congenital ptosis, in the hands of experienced surgeons, depend on two conditions: (1) the nature of the ptosis present and (2) the type of operation selected. This study, therefore, is designed to simplify the classification of congenital ptosis and to assist the surgeon in selecting the proper procedure for each type of ptosis.

This classification of ptosis is based on a personal survey of the hospital records of 200 consecutive cases of ptosis seen at the Institute of Ophthalmology, Presbyterian Hospital of New York City, during the past fifteen years. The original preoperative observations were made by various members of the attending and resident staffs. In all cases the vision was recorded for each eye, when possible; the vertical widths, and sometimes the lengths, of the two fissures were measured, both with and without assistance of the frontalis muscle; the movements of the extraocular muscles were carefully examined, especially those of the superior rectus; the presence or absence of function of the levator palpebrae was noted in all cases, and the position of the upper lid fold in each eye was often also noted. The cocaine test, to determine the function of Müller's muscle in the upper lid, was rarely made because, in the few cases in which this test was done, it was of no practical value in indicating what operation should be performed. Moreover, tests for corneal sensitivity and measurements of the width of the upper tarsus were seldom made because most patients were children. Because of lack of cooperation in some cases, especially in young children, it was difficult or impossible to be certain that the function of the superior rectus was entirely normal on the side of the ptosis because the ptotic lid often could not be adequately elevated manually to expose the cornea. In other cases it was difficult to ascribe the limitation of motility to any group of muscles. Cases in which the superior oblique and the external rectus were the only fully active extraocular muscles were considered instances of congenital paralysis of the third nerve. In other cases some weakness of all

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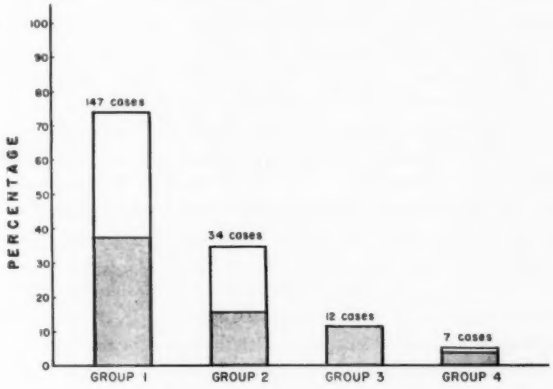
the extraocular muscles was present. Such a condition was considered due to congenital aplasia of all the extraocular muscles. In 1 of these cases operation revealed no elasticity of the inferior rectus muscle, presumably the result of congenital fibrosis. Cases of ptosis associated with Duane's retraction syndrome were not included in this series, for in this syndrome the ptosis is due to retraction of the globe and not to weakness of the levator muscle. No cases of acquired ptosis were included in this survey.

CLASSIFICATION OF PTOSIS

Ptosis may be classified in various ways, in accordance with the purpose the classification is designed to serve. The purpose of the



Classification of 200 cases of congenital ptosis.

Group 1 includes patients with a normal superior rectus muscle; group 2, patients with a weak homolateral superior rectus muscle either alone or combined with a weak homolateral inferior oblique; group 3, patients with the jaw-winking phenomenon, and group 4, patients with blepharophimosis. The clear rectangles indicate patients without function of the levator palpebrae, and the black rectangles, patients with normal function of the levator muscle.

present classification is to assist the surgeon in selecting the proper operation for each type of congenital ptosis. Careful examination of a number of patients will show that any case of congenital ptosis may be placed in one of four groups (chart): group 1, ptosis with normal function of the superior rectus muscle; group 2, ptosis with weakness of elevation due either to weakness of the superior rectus muscle alone or to weakness of the superior rectus and the inferior oblique muscles combined; group 3, ptosis associated with the jaw-winking phenomenon of Marcus Gunn, and group 4, ptosis associated with blepharophimosis (chart).

Group 1 was made up of 147 cases of congenital ptosis in which no weakness of the superior rectus or the inferior oblique muscle was noted. Therefore, in about 73.5 per cent of the entire series of cases of congenital ptosis ocular elevation was normal. Of the 147 cases, 105 were of unilateral and 42 of bilateral ptosis. Among the 105 cases of unilateral ptosis there were 1 case of exotropia, 5 cases of esotropia, 3 cases of overaction of the homolateral inferior oblique, 1 case of weakness of the homolateral inferior rectus and 1 case of overaction of each superior oblique muscle. Of the 42 cases of bilateral ptosis with normal elevation of the extraocular muscles, there were 2 cases of exotropia and 1 case of esotropia. Of the 147 cases in group 1, a complicating anomaly of the horizontal or vertical extraocular muscles was present in only 14 cases, or about 10 per cent.

Group 2 comprised 34 cases (or 17 per cent of the 200 cases) of ptosis associated with weakness of one or both of the homolateral extraocular elevator muscles. Of the 34 cases, weakness of the superior rectus alone was a complication in 10, being unilateral in 8 cases and bilateral in 2 cases. Of the 8 cases of unilateral ptosis with weakness of the homolateral superior rectus muscle, there were 3 of exotropia and 1 of esotropia. Of the 2 cases of bilateral ptosis with weakness of the superior rectus alone, 1 was of esotropia.

In about 12 per cent (24 cases) of the 200 cases there was a combined weakness of both the superior rectus and the inferior oblique muscle on the side of ptosis. Of the 24 cases 19 were of the unilateral and 5 of the bilateral form. The cases of unilateral involvement included 1 of exotropia, 1 of esotropia, 1 of proved fibrosis of the inferior rectus, 3 of what was thought to be a congenital paralysis of the third cranial nerve and 1 of weakness of all the extraocular muscles. Of the 5 cases of bilateral ptosis associated with bilateral weakness of the superior rectus and the inferior oblique muscles, paralysis of the third nerve was a further complication in 1 and weakness of all the extraocular muscles in 2.

It should be noted that in about 50 per cent (15 of 34) of the cases in group 2 the ptosis was complicated by some anomaly of the extraocular muscles besides the weakness of the superior rectus and/or the inferior oblique. In group 1, this complication was present in only about 10 per cent of the cases. This observation tends to show that if the vertically acting extraocular muscles are affected in ptosis, the horizontally acting muscles are more likely to be affected also, thus complicating the surgical correction.

Group 3 consisted of 12 cases of the jaw-winking (Marcus Gunn) phenomenon and comprised 6 per cent of the entire series of 200 cases. In all these cases the ptosis was unilateral, no cases of the

bilateral jaw-winking syndrome having ever been observed. In 5 of the 12 cases, the ptosis was uncomplicated by weakness of the superior rectus or the inferior oblique muscle; in 4 cases the superior rectus alone was weak (in 1 of which there was a further complication of exotropia), and in 3 cases there was combined weakness of the superior rectus and the superior oblique muscle. In 1 of these 3 cases a proved fibrosis of the inferior rectus produced the clinical picture of weakness of elevation. It is interesting to note that in 7 (58 per cent) of the 12 cases of the Marcus Gunn phenomenon a complicating anomaly of the extraocular muscles was present.

Group 4 consisted of 7 cases of ptosis associated with blepharophimosis, comprising 3.5 per cent of the entire series of 200 cases. In such cases there are short palpebral fissures, an abnormally wide distance between the inner canthi over the bridge of the nose and abnormally formed, S-shaped lids. In 1 of these 7 cases overaction of each superior oblique was present.

Of the 200 cases, the ptosis was unilateral in 145 (72.5 per cent) and bilateral in 55 (27.5 per cent). Of the 200 cases 147 (73.5 per cent) were instances of simple ptosis, while in 53 (26.5 per cent) the ptosis was complicated by imbalances of the vertically or horizontally acting extraocular muscles, these imbalances were represented by 7 cases of exotropia, 10 cases of esotropia, 41 cases of assorted vertical imbalances, 4 cases of congenital paralysis of the third nerve and 2 cases in which all the extraocular muscles were weak.

These figures demonstrate that ptosis is often a complicated condition in which other abnormalities of the extraocular muscles requiring surgical correction may be present. Proper treatment requires that these additional factors be carefully considered along with the ptosis, in order that satisfactory results may be attained.

Of these 200 cases, resection of the levator muscle was performed in 107 (53.5 per cent), and some modification of the Parinaud-Motais operation for correction of the ptosis, in 93 (46.5 per cent). Of the 107 cases in which the levator palpebrae was resected, the superior rectus muscle was normal in 76 (bilaterally in 21) (group 1), there were weakness of the superior rectus alone or combined with weakness of the inferior oblique in 23 (bilateral in 5) (group 2),[1] the jaw-winking phenomenon in 4 (group 3) and blepharophimosis in 4 cases (group 4). Of the 93 cases in which the Parinaud-Motais operation

1. In some of these 23 cases there may have been little or no action of the levator, but the chances of success seemed better for correction of the ptosis by resection of the levator than by suspension of the upper lid from the already weak superior rectus. Therefore, resection of the levator palpebrae in this group may have been done in some cases showing little or no action of the muscle clinically.

was performed, there were a normal superior rectus muscle in 71 (bilateral in 20) (group 1), weakness of the superior rectus alone or combined with weakness of the inferior oblique in 11 (bilateral in 1) (group 2),[2] the Marcus Gunn phenomenon in 8 cases (group 3) and blepharophimosis in 3 (group 4).[3]

COMMENT

Reports in the literature on the classification of ptosis are rare, the only comprehensive one being that of Spaeth,[4] who divided ptosis into 9 classes (page 357), and again into seven groups (page 364). He included in his classification acquired ptosis and ptosis associated with

Eighty-Eight Cases of Congenital Ptosis Reported by Spaeth Compared with 200 Similar Cases from the Institute of Ophthalmology

Group	Spaeth (88 Cases), Percentage	Berke (200 Cases), Percentage
1 Ptosis with normal superior rectus		
Unilateral	45.4	52.5
Bilateral	7.9	21.0
2 Ptosis with weakness of elevation		
Due to weakness of superior rectus alone		
Unilateral	29.9*	4.0
Bilateral	4.5	1.0
Due to combined weakness of superior rectus and inferior oblique		
Unilateral	5.6†	9.5
Bilateral	4.5†	2.5
3 Ptosis with jaw-winking	2.2‡	6.0
4 Ptosis with blepharophimosis	§	3.5
	100 (88 cases)	100 (200 cases)

* This percentage includes 5 cases of weakness of both superior rectus muscles with unilateral ptosis.

† Spaeth classified these cases as paresis of the third and fourth nerves.

‡ Spaeth mentioned the jaw-winking phenomenon in his classification but did not cite the number or percentage of cases seen; but, judging from the rest of his figures cited, it must be about 2 per cent.

§ Spaeth did not classify blepharophimosis by itself.

Duane's retraction syndrome, types of ptosis which I have purposely omitted. Therefore, his percentages cannot be fairly compared with those given here. However, after 10 cases of acquired ptosis and 2 cases of Duane's retraction syndrome are eliminated from his series of 100 cases, 88 cases of congenital ptosis are available for statistical comparison with the 200 cases reported here. In the accompanying table, it will be noted that Spaeth did not find as many cases of

2. The Parinaud-Motais type of operation was usually not done when the superior rectus was weak except in cases in which the levator palpebrae was so weak as to result in failure, or in other cases in which a resection of the levator had already been done, with inadequate correction.

3. The results of some of these 200 operations will be reported later. Berke, R. N.: Mötais Parinaud Operation for Ptosis: Report of Thirty-Five Cases, Arch. Ophth. (to be published).

4. Spaeth, E. B.: Principles and Practice of Ophthalmic Surgery, Philadelphia, Lea & Febiger, 1944.

ptosis with normal superior rectus muscles as I did (group 1), the superior rectus muscles being normal in 53 per cent of his cases and weak in 44.5 per cent (group 2), as compared with 73.5 and 17 per cent respectively, for the present series of 200 cases. This apparent discrepancy may be accounted for by the difficulty one experiences in cases of slight weakness of the superior rectus in being certain in the presence of ptosis whether the superior rectus muscle is fully active, especially in young children, and by the fact that what one observer considers normal function, another will call slight or definite weakness. Moreover, some allowances must be made for the fact that the data in Spaeth's series were based on his own observations, whereas the clinical findings in the 200 cases reported here are the combined observations of several clinicians. The apparent discrepancy between Spaeth's findings and those reported here as to the bilaterality of ptosis (Spaeth found that in 7.9 per cent of the cases with a normal superior rectus the ptosis was bilateral, whereas the corresponding figure in my series was 21.0 per cent) may be due to the fact that it is sometimes difficult to be sure that both upper eyelids are not ptotic, especially when the ptosis is greater on one side. In such cases, in which the palpebral fissure on one side measures 7 mm., so that the upper lid uncovers the pupil, while that of the opposite side measures only 2 or 3 mm. and the lid completely covers the pupil, some surgeons would consider the ptosis bilateral and unequal and other observers would consider the ptosis unilateral. Until some universal standard is accepted for measuring ptosis, differences such as those under discussion will occur.

TREATMENT OF PTOSIS

The criteria for a perfect operation for ptosis have previously been listed [5] but may be recited here:

1. The curve of the margin of the upper lid should overlap the cornea equally on the two sides, covering the upper part of the cornea when the lids are normally open.

2. The margin of the lid should be a smooth curve and similar in the two eyes, with no tendency to form a notch, or Gothic arch, or to invert the lashes when the lids are wide open.

3. The superior palpebral crease should correspond on the two sides.

4. The eye should be capable of being widely opened and of being completely closed, both in forceful closure and in sleep.

5. Normal winking should be preserved.

5. Berke, R. N.: Blepharoptosis, Arch. Ophth. **34**:434-450 (Nov.-Dec.) 1945.

6. The vertical distance between the eyebrow and the margin of the upper lid should normally be the same in the two eyes.

7. The upper lid of each eye should move synchronously with the globe in all directions of gaze.

8. Diplopia or disturbing heterophoria should be absent.

In a consideration of the surgical treatment of ptosis, it is interesting to note that over thirty years ago Beard[6] stated: "All who have had much experience in this branch of ophthalmic surgery will agree that the results of ptosis operations, taken all in all, are far from brilliant." The same thing could be said today, in spite of the more than eighty surgical procedures proposed for the treatment of ptosis, and I believe it will have to be accepted that the surgical treatment of ptosis is still in many respects one of the unsolved problems of ophthalmology. In my opinion, there are three main reasons for this: (1) the inherent nature of ptosis, (2) selection of the wrong type of operation and (3) use of the wrong technic in doing the operation selected. Each of these factors plays an important part in the cosmetic and functional result, but I believe that the nature of the ptosis is the most important single factor in determining that result.

There is no better way to obtain an over-all picture of the inherent and diverse nature of congenital ptosis than to study and analyze statistically a large number of cases. The present study of 200 consecutive cases showed that all cases of congenital ptosis can be placed in one of four groups: group 1, cases with a normal homolateral superior rectus muscle only; group 2, cases with a weak superior rectus muscle; group 3, cases of ptosis with the jaw-winking phenomenon of Marcus Gunn, and group 4, cases of ptosis with blepharophimosis. The four groups were further subdivided into cases with and cases without function of the levator palpebrae (chart).

This classification is useful in the surgical treatment of ptosis because it indicates immediately what operation is most likely to be successful in correction of the ptosis. In group 1, for example, there were 147 cases, comprising 73.5 per cent of the entire series, in which the superior rectus muscle was normal. Of this number, 76, or 51.7 per cent had some function of the levator muscle, and 71, or 48.3 per cent, had no such function. Because resection of the levator is the operation of choice in all cases of ptosis in which this muscle is active, it was indicated in 51 per cent of the cases in group 1. Because the superior rectus was normal in the rest of the cases, some modification of the Parinaud-Motais operation could be carried out in them. All the cases in group 1, therefore, were instances of uncomplicated or simple

6. Beard, W. H.: Ophthalmic Surgery, Philadelphia, P. Blakiston's Son & Co., 1914, pp. 230-252.

ptosis, in which there existed no problem as to the type of operation indicated. If the levator muscle was active, it should be resected; if not, the superior rectus should be utilized to correct the ptosis. Whichever operation is done in such cases, the results should be uniformly good; and failure, when it occurs, must be attributed to selection of the wrong type of operation or to faulty technic in the performance of the operation selected. For example, resection of the levator is likely to fail if the levator is completely paralyzed or absent. Moreover, both operations will result in failure if incorrectly performed.

In group 2, there were 34 cases of congenital ptosis with weakness of the homolateral superior rectus alone or combined with weakness of the inferior oblique. Of this number, function of the levator was present in 23, or 63 per cent, and resection of the levator was the operation of choice in these cases. The 11 cases without function of the levator were problem cases because resection of the levator could not be done with reasonable hope of success, nor could the weak superior rectus be utilized for lifting the lid. In such cases, in which both the superior rectus and the levator are paralyzed, some surgeons utilize the lifting power of the frontalis muscle to support the lid.

Even cases with action of the levator muscle in group 2 were problem cases in some respects, because in several instances the hypotropia associated with ptosis required one or more operations to correct it. White [7] called this condition pseudoptosis because when the ptotic eye is used for fixation, the eyelid and the eyeball assume a more or less normal aspect in the primary position, while the upper lid and the cornea of the fellow eye shoot far up. White expressed the belief that in these cases the hypotropia should be corrected before correction of the ptosis is attempted. Wheeler [8] agreed with this thesis and resected the homolateral superior rectus and inferior oblique muscles when both muscles were weak, before performing one of the types of the Parinaud-Motais operation. Kirby [9] decided, however, after several unhappy results with this program, that it might have been better in some of his cases to suspend the lid from the frontalis muscle after correcting the hypotropia than to utilize the already weak superior rectus for this purpose.

Whatever is done for patients with ptosis and hypotropia requires several operations, and the results are nearly always disappointing.

7. White, J. W.: (*a*) The Choice of the Fixing Eye in Paralytic and Non-Paralytic Strabismus, Tr. Am. Ophth. Soc. **41**:319-324, 1943; (*b*) Paralysis of the Superior Rectus and the Inferior Oblique Muscle of the Same Eye, Arch. Ophth. **27**:366-371 (Feb.) 1942.

8. Wheeler, J. M.: Personal communication to the author.

9. Kirby, D. K.: Paralysis of Ocular Elevation With and Without Ptosis, Tr. Am. Ophth. Soc. **43**:218-239, 1945.

Failure, therefore, must be attributed to the nature of the ptosis and not to selection of the wrong operation or to faulty technic. Certainly, the surgeon cannot be expected to create a normally functioning upper lid and eyeball when some normal muscle tissue does not already exist.

In group 3 were 12 cases of the jaw-winking phenomenon of Marcus Gunn. In most of these cases the ptosis completely disappeared when the lower jaw was depressed or when it moved to the opposite side. With the jaw in this position, the upper lid often overshot the mark, especially when the subject was looking down, so that the sclera above the upper limbus was exposed. Even though the levator muscle was active, resection of this muscle was contraindicated because shortening of the levator muscle would only enhance the jaw-winking phenomenon. The most logical approach to the problem is that suggested by Dunnington,[10] Carroll[11] and Spaeth,[12] in which the jaw-winking phenomenon is cured by first performing a complete tenectomy on the levator muscle, thus abolishing the jaw-winking act and simultaneously converting what is usually partial ptosis to a complete one, and then, at the same time, correcting the ptosis thus produced by utilizing the lifting power of the superior rectus or the frontalis muscle. Unfortunately, the superior rectus is not always normal in these cases, the homolateral superior rectus muscle being weak in 5 of the 12 cases of the series and a weak superior rectus being combined with a weak inferior oblique muscle in 3 additional cases. Spaeth[12] stated the belief that in all cases of the jaw-winking phenomenon the lid should be suspended from the brow after the levator muscle is tenectomized. In these cases, the jaw-winking phenomenon and the ptosis can be corrected, but usually at the expense of producing some other deformity. If the frontalis muscle is used to support the upper lid, the forehead must be wrinkled and the brow elevated to raise the lid. If the superior rectus is utilized, the lagophthalmos and hypotropia develop. Thus, one is forced to correct one deformity by producing another, less conspicuous, one. This must be so because of the nature of the ptosis.

Group 4 comprised 7 cases of ptosis associated with blepharophimosis. In some of these cases there were in addition to the ptosis and the blepharophimosis, abnormal development of inner canthi. These cases are problem cases and require special consideration. Before the ptosis is corrected, the phimosis must be cured by lengthening the palpebral fissure. This can be partially accomplished by an external canthoplasty combined with an operation to shorten the distance between

10. Dunnington, J. H.: Personal communication to the author.

11. Carroll, F. C.: Personal communication to the author.

12. Spaeth, E. B.: The Marcus Gunn Phenomenon: Discussion, Presentation of Four Instances and Consideration of Its Surgical Correction, Am. J. Ophth. **30**:143-158, 1947.

the inner canthi. After the fissures have been lengthened, the ptosis should be corrected by resection of the levator if this muscle is active or, if the levator is paralyzed, by utilization of the lifting power of the superior rectus or the frontalis muscles.

Cases of this sort present one of the most difficult problems in correction, and whatever functional or cosmetic improvement the surgeon can achieve must be considered an accomplishment. Since the surgeon is not supplied with adequate structures to work on, his failure to correct the defects satisfactorily must be attributed to the nature of the ptosis, and not to faulty judgment or technic.

SUMMARY AND CONCLUSIONS

A statistical study has been made of 200 consecutive cases of congenital ptosis seen at the Institute of Ophthalmology during the past fifteen years. Of the 200 cases, there were normal superior rectus muscles in 147 (73.5 per cent), weakness of the homolateral superior rectus alone or combined with weakness of the homolateral inferior oblique in 34 (17 per cent), the jaw-winking phenomenon of Marcus Gunn in 12 (6 per cent) and ptosis associated with blepharophimosis in 7 (3.5 per cent). Of the 200 cases, the ptosis was unilateral in 145 (72.5 per cent) and bilateral in 55 (27.5 per cent), simple in 147 (73.5 per cent) and complicated by horizontal or vertical anomalies in 53 (26.5 per cent). In 107 (53.5 per cent) of the 200 cases, sufficient action of the levator muscle existed to justify resection of the muscle as the operation of choice, while in 93 cases (46.5 per cent) there was no such function and the patients were candidates for some modification of the Motais-Parinaud operation or for the frontalis type of procedure.

This classification of congenital ptosis is useful in that it gives an over-all picture of the complicated nature of ptosis and, at the same time, is helpful to the surgeon in selecting the proper surgical procedure. It also gives him some idea of what to expect cosmetically and functionally from operations for the various types of congenital ptosis.

In the hands of experienced surgeons inadequate cosmetic and functional correction of ptosis depends on the inherent complicated nature of the ptosis rather than on faulty judgment or technic. Therefore, one should not expect perfection in every case of ptosis because the cosmetic and functional result in each case must be judged on the the nature of the ptosis present.

140 Union Street.

Ophthalmologic Reviews

INTRAORBITAL TUMORS

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A CORRELATION of the clinical data with the histologic features is especially important in the case of intraorbital tumors, for, to a greater extent than in most ophthalmic diseases, the treatment and prognosis are determined by the results of microscopic examination. Accordingly, it is the purpose of this report to summarize the data relating to the pathology, semeiology and history of the disease in a series of 222 cases of tumors, selected wholly on the basis of their situation in the orbit, from the collection in the Registry of Ophthalmic Pathology, of the Army Institute of Pathology. Since the material was available only as gross and microscopic preparations, emphasis will necessarily be on the pathology; in this way, this study differs from those of Birch-Hirschfeld [1] and Reese.[1a]

The structure and development of the orbital contents suggest the possibility of a wide variety of tumors. The incidence of each type in this series is indicated in the accompanying table.

PRIMARY TUMORS

In this series, 184 tumors, both benign and malignant, were primary in the orbit, and only 38 were secondary. The primary tumors have been classified according to their origin and will be discussed in the order of this grouping.

MESENCHYMAL TUMORS

Connective Tissue Tumors.—The connective tissue tumors in this series numbered 43. In 30 cases the tumors were benign, and, of these, the lipoma was the commonest variety, being present in 19 cases. Lipomas were usually situated anteriorly in the orbit, and, except in 2 cases, in which the tumor was in a posterior location, the presenting symptom was that of a mass. Ptosis in 2 cases indicated that the lid

From the Registry of Ophthalmic Pathology, Army Institute of Pathology, Washington, D. C.

Read before the Section on Ophthalmology of the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 24, 1948.

1. Birch-Hirschfeld, A., in Graefe, T., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, Berlin, Julius Springer, 1930, vol. 1, pt. 1.

1a. Reese, A. B.: Orbital Tumors and Their Surgical Treatment, Am. J. Ophth. **24**:386-394 (April); 497-502 (May) 1941.

was also involved. In the 2 cases of posterior tumor the lipoma was discovered when the eye was enucleated because of exposure keratitis. In another case enucleation was performed because of a macular mass in a blind eye, and a large lipoma was noted surrounding the optic nerve (fig. 1 *A*).

Intraorbital Tumors

Primary Tumors	
I. Mesenchymal origin	
A. Connective tissue	
Benign	
Lipoma	19
Osteoma	5
Fibrolipoma	2
Fibroma	2
Chondroma	1
Rhabdomyoma	1
Malignant	
Undifferentiated sarcoma	7
Rhabdomyosarcoma	4
Fibrosarcoma	2
B. Vascular system	
Benign	
Hemangioma	24
Malignant	
Angiosarcoma	1
C. Hematopoietic system	
Lymphoma, lymphosarcoma	22
Hodgkin's disease	2
Plasmocytoma	1
II. Epithelial origin	
Mixed tumor	25
III. Neural and meningeal origin	
Benign	
Neurofibroma	17
Meningioma	17
Glioma	5
Malignant	
Neurofibrosarcoma	9
IV. Developmental fault	
Dermoid	17
Teratoma	1
Total	184
Secondary Tumors	
Carcinoma	24
Neuroblastoma	6
Melanoma	6
Pituitary adenoma	1
Retinoblastoma	1
Total	38
Total series of tumors	222

The tumor was bilateral in 2 cases, both the patients being over 58 years of age. There was no other noteworthy feature in the age or sex distribution. The tumor had been noticed since birth in 4 patients, the oldest of whom was 23 years of age. In all but 2 cases the lipoma was treated by simple excision of the mass; the globe, as well as the mass, was removed in 2 cases.

Pathologically, the lipomas were composed of lobules of adult fat. A capsule was not apparent histologically; hence the tumors were indistinguishable from normal orbital fat, and the diagnosis of tumor

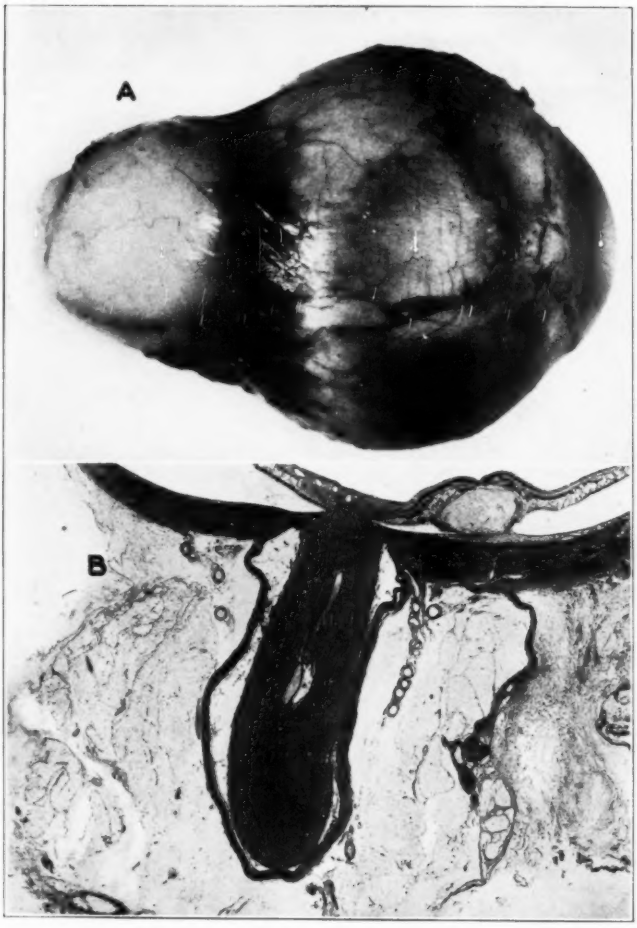

Fig. 1.—Lipoma. (*A*) Gross photograph, showing posterior position of tumor A.I.P. neg. no. 181038; (*B*) photomicrograph, showing tumor surrounding optic nerve and mass of organized submacular hemorrhage × 10, A.I.P. neg. no. 101099.

was based on the surgeon's statement. The microscopic appearance of the tumor which surrounded the optic nerve is shown in figure 1 *B*. In 1 instance macrophages invading the mass represented a reaction to degenerating lipid.

Classified as osteoma was an abnormal bony proliferation in the orbit in 5 cases (fig. 2*A*). In 1 case the lesion was associated with a dermoid and in a second with a meningioma. In 3 instances the masses were autonomous tumors; in the roentgenogram 2 of these appeared to compromise the frontal sinus.

Two tumors, containing a considerable quantity of fibrous tissue as part of the neoplastic process in addition to the fat cells, were regarded as fibrolipomas.

Two benign tumors of connective tissue origin which were entirely fibrous in nature were classified as fibromas. One of these was situated anteriorly and was composed of dense collagenous tissue. It was attached to, and probably arose in, the tendon of an extraocular muscle. The second fibroma, the presence of which was suspected because of increasingly choked disk, was somewhat more cellular and edematous and was observed to have arisen in the dural sheath of the optic nerve (fig. 2*B*).

One tumor of cartilaginous nature, a chondroma, was attached to the superior orbital margin.

A tumor warranting more detailed comment because of its rarity was a rhabdomyoma which had occurred in the orbit of an 18 year old Negro. The presenting complaint was exophthalmos, which had increased 8 mm. in seven years. At operation it was noted that the tumor was attached to the superior rectus muscle and filled the upper portion of the orbit. It measured 30 by 17 by 12 mm. Microscopically, the neoplasm consisted of abnormal striated muscle cells (fig. 2*C*), the fibers of which were irregularly disposed and hence sectioned in random planes, in contrast to the regular arrangement of the strands in normal rectus muscle. In view of the absence of evidence of inflammation, recent or old, and the disparity between the size of the lesion and that of normal muscle, this mass was considered neoplastic, and not degenerative or inflammatory. Because of the maturity of the cells it was presumed to be benign.

In addition to the 30 benign tumors described, there were 13 malignant tumors of connective tissue origin. In contrast to the generally anterior situation of the benign tumors, the malignant tumors were noted posteriorly in the orbit. Exophthalmos was the prominent symptom in 11 cases, and in 1 case there was associated ptosis, apparently of sudden onset. All but 3 of the patients were less than 20 years of age, and one-half were less than 12 years of age.

Seven orbital tumors were classified as undifferentiated sarcomas. Pleomorphism and hyperchromatism of cells in stroma having connective tissue features characterized these tumors; mitotic figures were not uncommon, and occasional giant and other bizarre forms were present. Occasional vacuoles within the cells took a stain for fat, but

the presence of fat is common in rapidly growing sarcomas, often as a degenerative product, and does not alone indicate an origin in lipid tissue or a differentiation toward mature fat cells. Three of the 7 patients with an undifferentiated sarcoma died in from three to twenty-four months after operation; 2 were alive with recurrence after

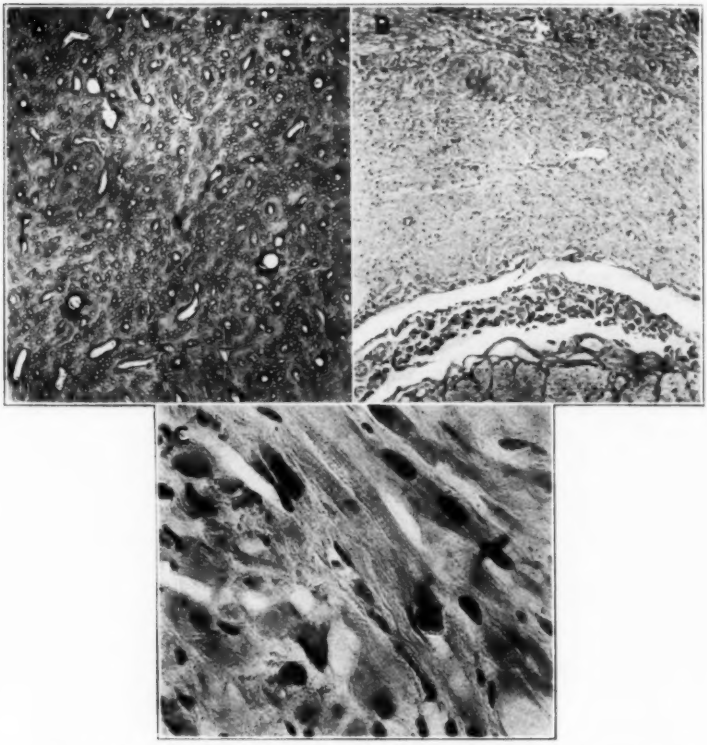

Fig. 2.—(*A*) Osteoma, × 40, A.I.P. neg. no. 104581; (*B*) dural fibroma, × 40, A.I.P. 101098; (*C*) rhabdomyoma, × 300, A.I.P. neg. no. 101097.

eight and eighteen months, respectively, and 1 was alive and well five years after operation. The status of 1 patient was unknown.

Four of the 13 malignant tumors included in the connective tissue series were regarded as rhabdomyosarcoma, since they appeared to have arisen in striated muscle. All the patients having this tumor were less than 10 years of age. Histologically, the tumors were characterized by cross striations in the cytoplasm, which was eosinophilic, often

abundant and occasionally terminating in ribbon-like ends. The nuclei were often large, occasionally of giant size, rarely multiple (fig. 3).

Two patients with rhabdomyosarcoma died within a year, and the other 2 were alive ten and fourteen years after operation. The clinical impression of the presence of a capsule in the specimen from a patient who died was apparently of little prognostic value. It is probable that the structure was a pseudocapsule, resulting from compression of the surrounding tissue. In this instance, the first recurrence was noted within four months, and a few months after the second excision the

Fig. 3.—Rhabdomyosarcoma, showing anaplasia and cross striations, × 450, A.I.P. neg. no. 101203.

orbit was filled with a mass, which continued to grow until it was more than 4 inches (10 cm.) in diameter. Autopsy revealed widespread metastases.

Two other malignant tumors of connective tissue, fibrosarcomas, were composed of collagen-producing cells. One of the patients was well three and one-half years after operation, and the other had noted recurrence ten months after operation.

In summary, the benign connective tissue tumors were characteristically of random age distribution and were situated anteriorly in the orbit, and the majority were lipomatous. In contrast, the malignant

tumors occurred in young patients and, arising posteriorly in the orbit, caused exophthalmos. The cellular immaturity of the malignant tumors often precluded classification of cell types. The median duration of symptoms related to benign tumors was three years, whereas one-half the malignant tumors had produced symptoms less than two months before the patient consulted the surgeon. Approximately one third of the patients with malignant tumors died early in the course of the disease; one-third are living but are known to have recurrence, and one-third are known to be living and well at least five years after removal of the tumor. In view of the poor results of therapy, which was conservative in the majority of cases in this series, it would seem that if the diagnosis of sarcoma is confirmed microscopically, early exenteration of the orbit might better the prognosis.

Tumors of Vascular Origin.—The 25 neoplasms of the vascular system comprised almost 15 per cent of the primary orbital tumors. Eleven of these were noted in patients under 3 years of age. Many of the vascular tumors were probably congenital, although the initial symptoms often became evident after birth, and in 1 patient as late as at 60 years of age. One-half the lesions were situated anteriorly in the orbit, and one-half caused exophthalmos. Information was not available as to whether there were coexistent angiomas of the skin.

Histologically, these tumors were disposed in a continuum from a structure which contained well developed cavernous channels (cavernous hemangioma), through neoplasms with smaller vessels (capillary hemangioma) to those characterized by high cellularity and small, inconstant blood channels (hemangioendothelioma, hemangioblastoma or, in the most malignant form, angiosarcoma).

Sixteen tumors in this group were of the cavernous variety, in which connective tissue trabeculae of varying thickness separated endothelium-lined vascular channels of inconstant size, containing blood (fig. 4 *A*). In 2 specimens, all of the spaces were relatively small, of the order of capillaries (fig. 4 *B*). In 1 of these, additional connective tissue trabeculae divided the tumor into lobules; in the other, the tumor was situated within the substance of the lacrimal gland. In 3 tumors there was moderate diffuse fibrosis between the endothelial cells, among which were small vascular channels. This presumably regressive change produces the "sclerosing hemangioma." In 3 of the remaining specimens, small vascular channels, in which it was often difficult to discern erythrocytes, traversed the sheets of endothelial cells. These cells were composed of scanty cytoplasm and oval, vesicular nuclei, in which occasional nucleoli were noted. These densely cellular tumors, which are, however, cytologically quiescent and carry no implication of malignancy, represent the benign hemangioendothelioma, or juvenile hemangioma (fig. 4 *C*).

This classification is based on the predominant histologic appearance. In some specimens, however, features of more than one type were present, dependent perhaps on the age or differentiation of the tumor. The specimen which best illustrates this phenomenon is one

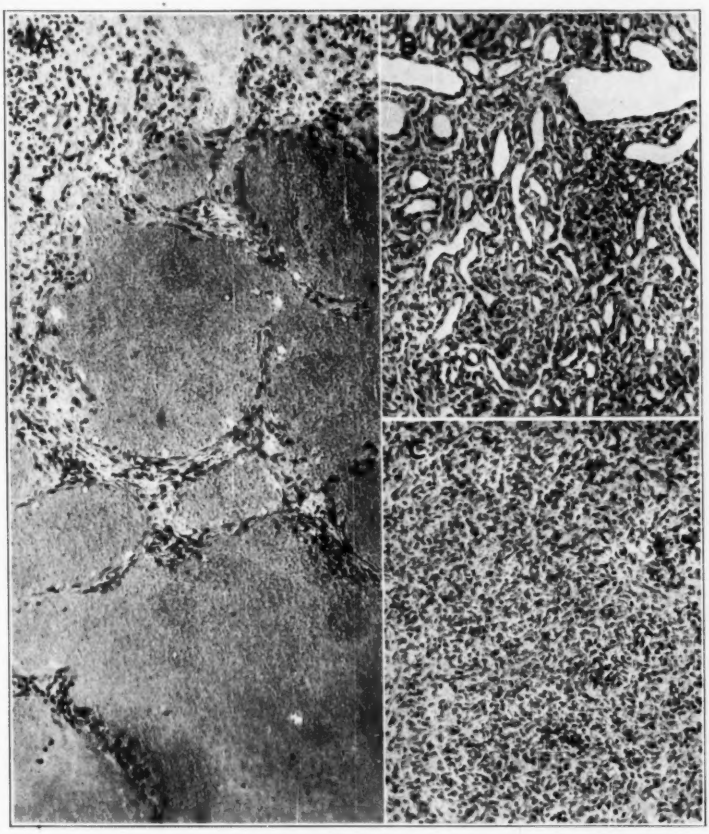

Fig. 4.—(*A*) Cavernous hemangioma, × 114, A.I.P. neg. no. 104514; (*B*) capillary hemangioma, × 135, A.I.P. neg. no. 100702; (*C*) hemangioendothelioma, benign (juvenile hemangioma), × 160, A.I.P. neg. no. 100701.

in which evidence of cytologic activity, including numerous mitotic figures, suggests malignant potentialities of the tumor, an angiosarcoma, although there is no follow-up information in this recently registered case. Figure 5, of low magnification, includes a perforated corneal

ulcer and a massive tumor made up of both cavernous and densely cellular areas. The cavernous areas, in which some of the spaces contained a protein material similar to that seen in the lymphangioma, are shown under higher magnification in figure 6 *A*. In other fields, smaller channels and highly cellular areas were noted, and within the sheets of endothelial cells clusters were present which simulated the capillary buds seen in granulation tissue (fig. 6 *B*). Since the potentiality of a tumor is determined by its most active element, tumors such as the one just described were classified as hemangioendotheliomas. The invasive tendency of this type of tumor is illustrated by the

Fig. 5.—Hemangioendothelioma, malignant (angiosarcoma), × 2, A.I.P. neg. no. 102435.

extension of a portion of the tumor into the bony orbital wall (fig. 6 *C*) and by invasion of voluntary muscle (fig. 7).

Tumors of the vascular system are rarely malignant, and a metastasizing angioma was not included in this series. More frequently, because of the technical difficulty of orbital surgery, there remains a modicum of tumor, especially of the highly cellular forms, leading to clinical recurrence. The scanty follow-up data were of no assistance in confirming these generally accepted principles.

Tumors of Hematopoietic System.—There were 25 tumors derived from the blood-forming tissues, excluding, of course, the many masses

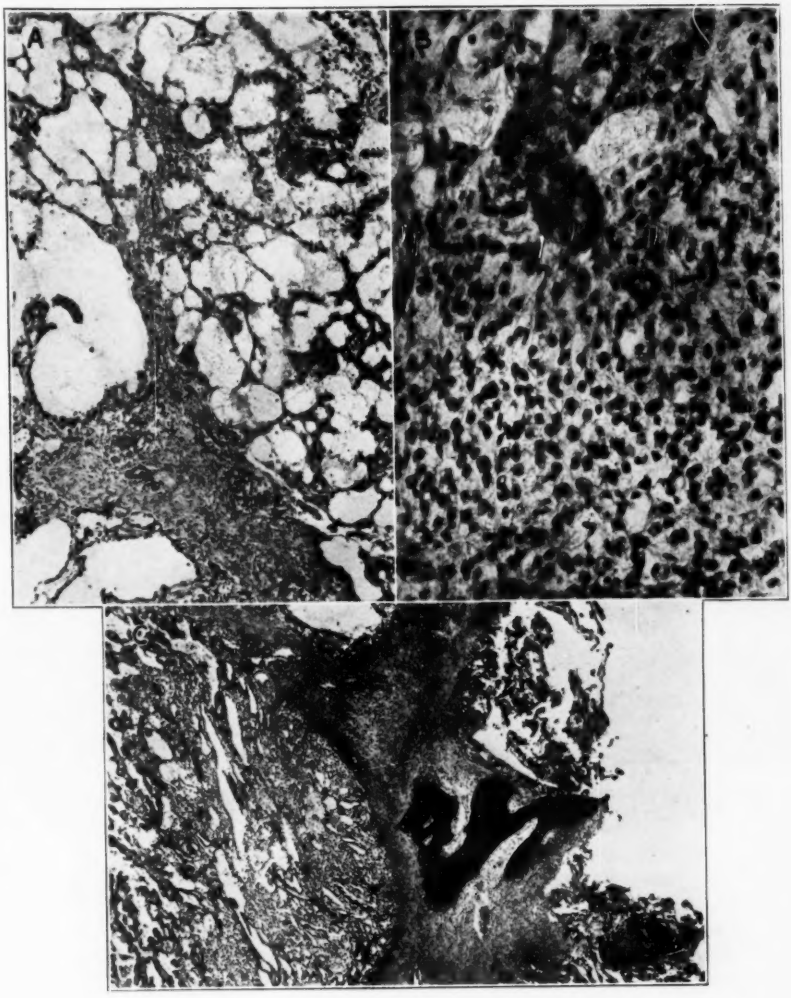

Fig. 6.—Angiosarcoma. (*A*) Large spaces containing blood and protein material, × 60, A.I.P. neg. no. 102438; (*B*) cellular area with cluster of cells similar to capillary bed, × 210, A.I.P. neg. no. 102433; (*C*) area of invasion of bone, × 40, A.I.P. neg. no. 102434.

limited to the conjunctiva. Only 4 occurred in patients less than 40 years of age. Of the 21 patients on whom clinical information is available, 11 complained of exophthalmos and 10 of a mass. Patients with anteriorly situated tumors sought medical assistance in most instances in less than five months after the mass was first noted, whereas in over one-half the cases in which exophthalmos was the initial complaint the symptoms had been present for more than one year.

Except for Hodgkin's disease and plasmocytoma, which can be separated histologically from the group, tumors of the lymphocytic series are classified with difficulty. Elsewhere in the body the integrity

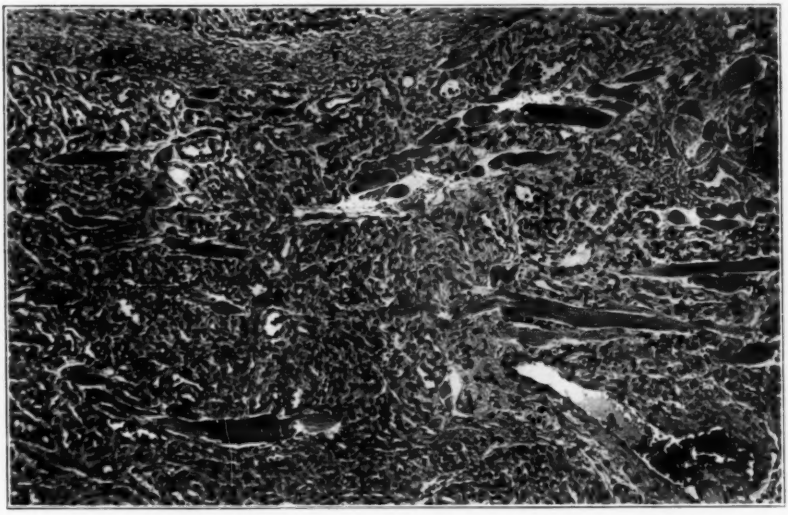

Fig. 7.—Hemangioendothelioma invading rectus muscle, × 115, A.I.P. neg. no. 104582.

of the architecture of lymph nodes is an important criterion. In the orbit, however, nodes are not normally present, and the histologic distinction of lymphocytic infiltration, lymphatic lymphadenosis and benign and malignant lymphomatoid tumors about the eye is often difficult. The question of separating the benign from the malignant variety is further confused by the slow course of even some of the lymphosarcomas which may become multicentric, by the occasional "cure" of an isolated lesion of lymphosarcoma by excision and by the high radiosensitivity of both benign and malignant lymphomas. Unfortunately, the follow-up data on the cases in this series are too limited to be significant, although some of the information may be of interest.

Four of the 25 excluded tumors were classified as "benign lymphomas." The age distribution and symptoms were not significantly different from those of the malignant lesions. In these tumors the type cell was uniformly the small, mature lymphocyte; well formed or suggestive follicles were occasionally present.

Although previously the differentiation of the types of lymphosarcoma has been labored, the growing impression among pathologists

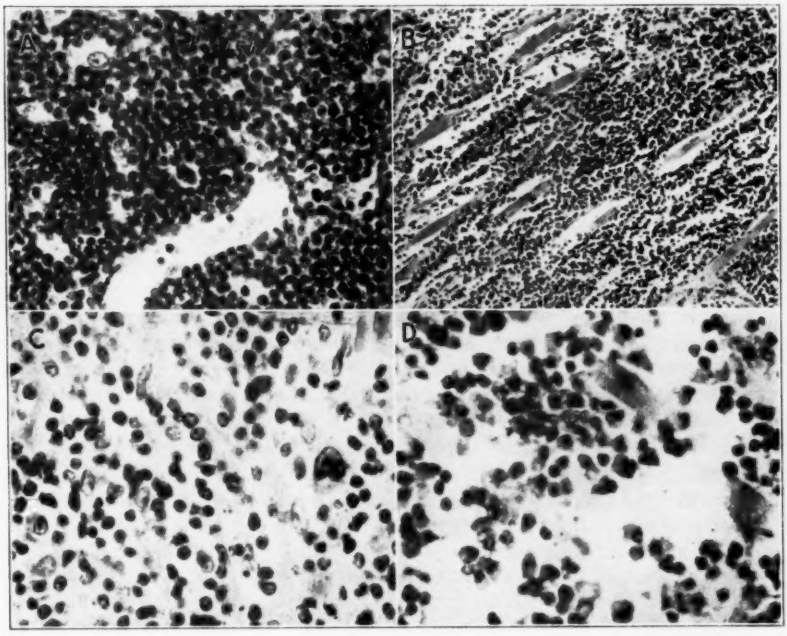

Fig. 8.—Hematopoietic tumors. (*A*) Lymphosarcoma with mitotic activity, × 475, A.I.P. neg. no. 101231; (*B*) lymphosarcoma infiltrating muscle, × 160, A.I.P. neg. no. 101202; (*C*) Hodgkin's disease, × 605, A.I.P. neg. no 104576; (*D*) plasmocytoma, × 720, A.I.P. neg. no. 104580.

is that this delicate cataloguing is somewhat artificial, since several of the types appear to be merely stages of the same disease. More than one type may be found in the same patient. The term lymphosarcoma is used here to include the lymphoblastic, lymphocytic and reticulum cell varieties. Eighteen tumors were included in the lymphosarcoma group. In 2 cases there were abnormalities of the peripheral blood. In 1 case the large mononuclear cells in the circulating blood

were interpreted by most of the Registry consultants as those of monocytic leukemia. In the second, lymphatic leukemia was associated with the orbital infiltration, which, as in all the other cases, was the only apparent site of disease at the time of operation. Histologically, these tumors were characterized by dense infiltrations of lymphocytes at different stages of maturation. Mitotic figures were common (fig. 8*A*). Inconstant amounts of argyrophil reticulum were noted, and in the reticulum cell type an intimate relationship with the tumor cell was occasionally demonstrable. In many of the microscopic preparations lymphoid tissue invaded muscle and fat, indicating at least a locally invasive propensity (fig. 8*B*).

There was 1 case of typical Hodgkin's disease. The Sternberg-Reed cell is shown in figure 8*C*. One tumor in the lymphomatoid group, characterized by pronounced pleomorphism, cells suggestive of the Dorothy Reed type and a peculiar desmoplastic reaction, was regarded as sclerosing Hodgkin's sarcoma.

The remaining tumor in this group was composed of sheets of mature plasma cells and was thought to be an isolated plasmocytoma (fig. 8*D*). This was the only specimen which could be related to the myeloid series.

In this series, all the lymphomatoid tumors were, at least initially, isolated lesions. Evidence of generalized disease at the time the patient sought medical aid was noted only in the 2 instances in which an abnormal blood picture was described. It is now generally recognized that the leukemias may be merely other phases in the development of these diseases and that lymphosarcoma may occur with or without peripheral changes in the blood.

In this group of orbital lymphomas, death ensued in from two to nine months in 4 of the 7 cases in which the follow-up information was available. One patient, for example, had complained of increasing exophthalmos of five months' duration and died two months after operation, when generalized lymphadenopathy was noted. Two patients were well two and six years, respectively, after operation. One patient, with leukemia, was alive five years after operation with generalized glandular enlargement. No data were available in the other cases.

EPITHELIAL TUMORS

Mixed Tumor of the Lacrimal Gland.—There were 25 mixed tumors of the orbit. They are included with the tumors of epithelial origin, since this concept of the histogenesis is most widely accepted, although others have been suggested.

The mixed tumor, which arises in the serous glands of the head, including the major and minor salivary glands, is included with orbital tumors by virtue of its occurrence in the lacrimal gland. McFarland

presented an excellent analysis of a group of these tumors of the salivary glands and a discussion of their nature.[1b] The use of such terms as enchondroma, cylindroma, enclavoma, compounded tumor, endothelioma, basal cell carcinoma, sarcoma and epithelioma indicate the many histogenetic concepts. More recently, the theory of the notochordal origin of these tumors, presented by Hellwig,[2] and the designation of mucoepidermoid tumors by Stewart and his associates [3] are noteworthy.

In the 25 cases of this tumor the ages of the patients ranged from 18 to 76 years. In 12 cases proptosis was the presenting complaint; in 9 it was of less than one year's duration, and in others it had been present for two, five and seven years, respectively. In 13 other cases the presence of a noticeable mass was the initial symptom. Such masses existed for from one to two years before surgical treatment. The absence of tearing was noted in 1 case. Roentgenograms were available in 2 cases; in 1 case they indicated erosion of the supraorbital ridge, and in the other, no bony change. In 2 cases of recurrence erosion of bone was noted, and in 1 case there was massive invasion of the base of the cranium and the temporal fossa.

Pathologically, all the specimens fulfilled the diagnostic criterion of being comprised of both epithelial and mesenchyma-like elements. Eighteen of the tumors were considered typical and were composed of cuboidal epithelium and loose, chondromatoid connective tissue (fig. 9 *A*). In the most differentiated variety, dilated acini and tubules, with walls usually made up of two layers of epithelium, were separated by lightly basophilic, fibrillar connective tissue, in which the cellular elements varied from spindle to stellate configuration. This myxoid material and some of the contents of the glandular structures may stain red with mucicarmine. In 5 specimens the presence of cystic spaces suggested the apperance of the Brooke type of basal cell carcinoma of the skin, the epithelioma adenoides cysticum (fig. 9 *B*). Among other pathologic variants in 1 specimen, in addition to these cystic areas, there were large cellular sheets which were similar to those in the Krompecher type of basal cell carcinoma, or basaloma (fig. 9 *C*). In 1 specimen, which was otherwise typical, keratin cysts were noted in the cellular areas (fig. 9 *D*). The abrupt transition from epithelium to keratin and the presence of calcium were reminiscent of the calcifying

1b. McFarland, J.: Three Hundred Mixed Tumors of the Salivary Glands of Which Sixty-Nine Recurred, Surg., Gynec. & Obst. **63**:457, 1936; Histopathologic Prognosis of Salivary Gland Mixed Tumors, Am. J. M. Sc. **203**:502, 1942.

2. Hellwig, C. A.: Mixed Tumors of the Salivary Glands, Arch. Path. **40**:1 (July) 1945.

3. Stewart, F. W.; Foote, F. W., and Becker, W. F.: Muco-Epidermoid Tumors of Salivary Glands, Ann. Surg. **122**:820, 1945.

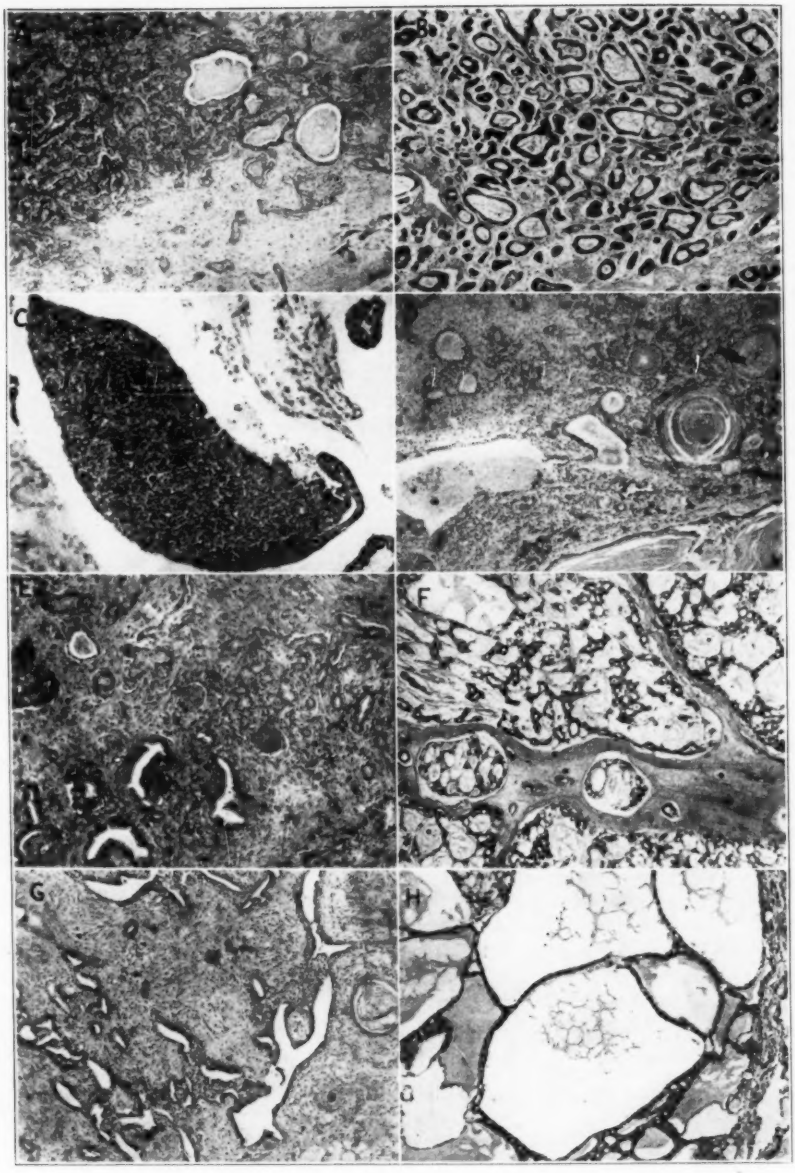

Fig. 9.—Mixed tumors. (*A*) Archetype, × 60, A.I.P. neg. no. 100958; (*B*) tumor resembling epithelioma adenoides cysticum of the skin, × 61, A.I.P. neg. no. 100956; (*C*) tumor resembling Krompecher type of basal cell carcinoma, × 60, A.I.P. neg. no. 100955; (*D*) tumor with accumulations of keratin, × 40, A.I.P. neg. no. 100959; (*E*) tumor containing nests of cells similar to squamous cell pearls, × 110, A.I.P. neg. no. 104572; (*F*) tumor simulating colloid carcinoma of intestinal tract, × 130, A.I.P. neg. no. 104578; (*G*) tumor resembling carcinoma of adenofibroma of breast, × 90, A.I.P. neg. no. 104577; (*H*) tumor containing large cystic spaces, × 90, A.I.P. neg. no. 104575.

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epithelioma of the skin. In another specimen, cellular nests similar to epithelial pearls were observed (fig. 9 *E*). One tumor, in which the mucinoid areas may have resulted from cellular degeneration (fig. 9 *F*), was very much like the colloid carcinoma of the breast or intestinal tract. Another resembled the adenofibroma of the breast (fig. 9 *G*). Large cystic spaces in the last specimen correlated with the cystic consistency noted clinically and accounted for the confusion with dermoid cyst (fig. 9 *H*).

Numerous subclassifications based on the morphologic features of these tumors have been suggested, but there is little evidence that there is any real difference between the types, and in this series they were all classified as mixed tumors. Multiple sections often revealed at least small areas of the mixed tumor prototype, even though the initial sections were somewhat anomalous. McFarland [1b] stated that "histologic variations among mixed tumors have no bearing upon prognosis." He reported tumors classified histologically as sarcoma which behaved clinically in a manner identical with the usual mixed variety. In 1 of his cases the primary tumor was described as carcinoma, but the recurrent growth was noted by the same pathologist to be a more typically mixed tumor.

In most of the cases in this group treatment was by simple excision of the tumor initially, but in at least 8 cases enucleation or exenteration was finally required.

Follow-up data are available in less than one-half the cases. In only 1 of these 10 cases was there no evidence of recurrence five years after operation, and in 9 cases a second operation was required within one to six years after the first. The records in 4 cases indicated only the initial recurrence; second recurrences were noted in 5 cases. Recurrence in 1 of the cases of morphologically typical tumor was first noted fifteen months after operation, and the neoplasm was removed three months later. In some areas of this mass there were cells containing an abundance of eosinophilic cytoplasm and large, nucleolated nuclei suggestive of squamous epithelium. Occasional bizarre forms, including multinucleated cells, were noted. The connective tissue stroma, composed of young fibroblasts, had lost its basophilic, myxoid appearance and represented merely the desmoplastic response to the epithelial growth (fig. 10 *A*). This was morphologically a squamous cell carcinoma arising in a typical mixed tumor.

McFarland reported a tumor with chondroid features in some areas and cellular structure typical of carcinoma in others. At autopsy only the histologically malignant moiety was noted in the metastatic masses. Sanders [4] also showed that only the epithelial constituent was present

4. Sanders, T. E.: Mixed Tumors of the Lacrimal Gland, Arch. Ophth. **21**: 239 (Feb.) 1939.

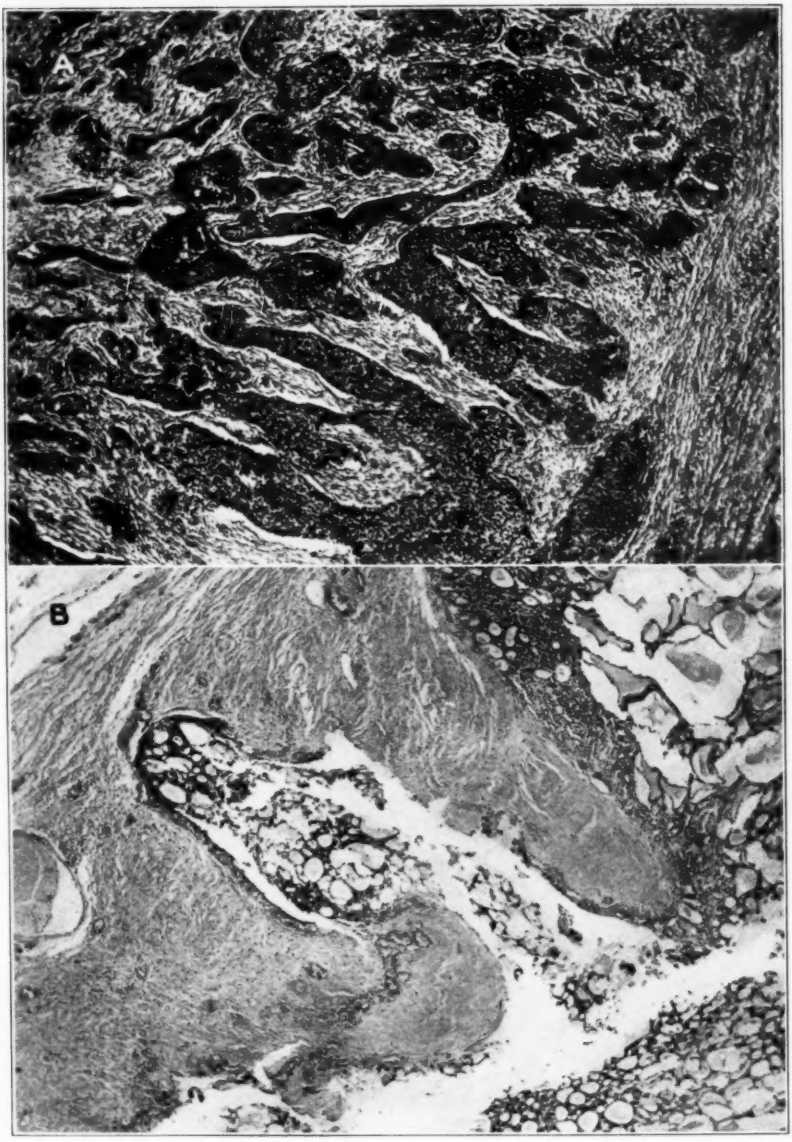

Fig. 10.—Mixed tumor. (*A*) Recurrence resembling squamous cell carcinoma, × 62, A.I.P. neg. no. 100957; (*B*) tumor cells invading capsule, × 55, A.I.P. neg. no. 104574.

in the tumor tissue which had invaded bone. The invasion of the fibrous capsule of one of the tumors by the epithelial elements is shown in figure 10 *B*.

The data gathered here suggest confirmation of Sanders' conclusion that mixed tumors of the lacrimal gland will recur if allowed sufficient time. It is conceivable that radical surgical treatment would preclude recurrence, and thus that early exenteration would be advisable.

NEURAL AND MENINGEAL TUMORS

In this section, tumors are considered which arise either from the supporting networks of the central and peripheral nervous systems or from the structures which cover the brain and spinal cord.

Neurofibroma.—Seventeen tumors in this series were related to peripheral nerves; specifically, they were thought to arise from the sheaths of the nerves. Since there is general agreement on neither the genesis of these tumors nor the significance of morphologic subclassification, all the benign, collagen-forming neurogenic tumors are classified as neurofibroma.

In 10 cases exophthalmos was the presenting symptom and had been noted for periods of from six months to thirteen years. In 4 instances the tumor lay anteriorly, and the duration of symptoms had been from only two weeks to five months. In 3 cases the situation of the tumor was not stated.

The 17 tumors may be divided into two morphologic types. In 10 tumors the cellular disposition was well defined and characteristic of neurofibroma. Verocay bodies were prominent in several specimens (fig. 11 *A*). These structures were made up of palisades of spindle cells separated by collagen. Tumors containing these structures have been known as schwannomas. In 2 of the tumors in which the cellular pattern was distinctive, a herringbone arrangement was prominent (fig. 11 *B*), and only in a few areas was there a suggestion of palisading. In 1 of the tumors, which arose from a long posterior ciliary nerve in its intraocular course, moderate pleomorphism suggested low grade malignancy (fig. 11 *C*). A recurrent orbital mass, which was removed four years later because of the suspected malignancy of the primary tumor, proved to be only an epidermal inclusion cyst and an amputation neuroma.

In 7 specimens the serpentine character of the collagen fibers and of the thin, delicate nuclei was the basis for the diagnosis (fig. 11 *D*). Microcystoid degeneration and edema (fig. 11 *E*) were the histologic representation of the consistency of the fibroma molle. Xanthoma cells, a reaction to degenerating lipid probably related to destruction of myelin, were common in the neurofibroma (fig. 11 *E*). In 1 specimen, three

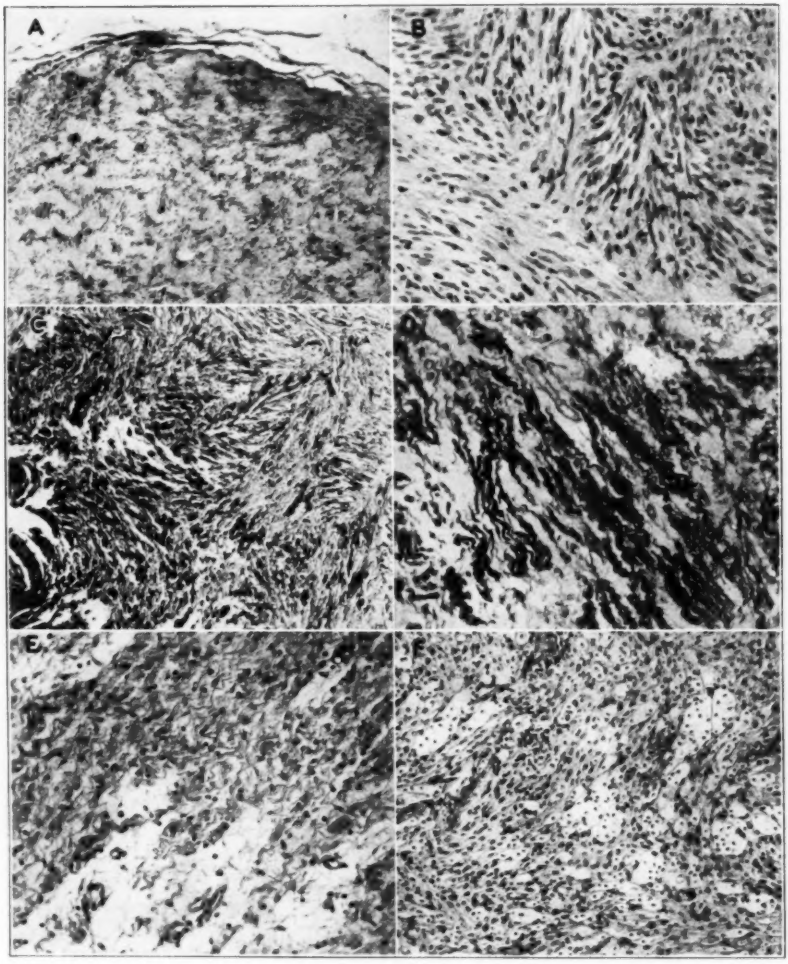

Fig. 11.—Neurofibroma. (*A*) Palisades of cells, × 80, A.I.P. neg. no. 100896; (*B*) herringbone arrangement, × 235, A.I.P. neg. no. 101283; (*C*) mild anaplasia, × 120, A.I.P. neg. no. 100894; (*D*) serpentine collagen fibers (Van Gieson stain), × 220, A.I.P. neg. no. 100895; (*E*) edematous tumor, × 150, A.I.P. neg. no. 100889; (*F*) xanthoma cells, × 115, A.I.P. neg. no. 101288.

characteristics of neurofibroma were noted: abortive Verocay bodies, serpentine fibers and edema (fig. 12 *A*). In a case of von Recklinghausen's disease (multiple neurofibromatosis) an orbital neurofibroma was present.

Meningioma.—Seventeen of the tumors in this series arose in the arachnoid which invests the brain and the optic nerve. Whether this sheath is of epiblastic or mesoblastic origin is controversial, although the cells, in their ability to produce bone and cartilage, unquestionably behave like mesenchymal tissue.

Since the work of Schmidt,[5] in 1902, it has been generally believed that intracranial meningiomas arise in the arachnoidal granulations. Analogous clusters of arachnoidal cells, which may eventually form psammoma bodies, are to be seen in normal optic nerve sheaths, and it is assumed, therefore, that some orbital meningiomas may arise from such clusters (fig. 12 *B* and *C*). Cushing and Eisenhardt[6] presented an excellent discussion of the subject, including the histogenesis.

A meningioma may involve the orbit in any of three ways: First, it may be primary in the sheath of Schwalbe; second, it may extend into and involve the sheath through the optic foramen from a site of origin in the basilar meninges, or, third, it may invade the orbit through the bony wall, usually the roof, without involving the coverings of the optic nerve.

From the therapeutic point of view, it is obviously of cardinal importance to know whether a tumor is entirely intraorbital or partly intracranial. Verhoeff[7] previously expressed the opinion that no case of primary intraorbital meningioma had been satisfactorily demonstrated. This is in agreement with evidence presented earlier by Pagenstecher,[8] in 1902, and by Dusaussay,[9] in 1875, each of whom reported a case of meningioma of the optic nerve in which small intracranial masses were observed at autopsy many years after orbital operation. In Dusaussay's case, the interval from operation to death was twenty-five years.

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5. Schmidt, M.: Ueber die Pacchionischen Granulationen und ihr Verhältniss zu den Sarcomen und Psammomen der Dura mater, Virchows Arch. f. path. Anat. **170**:429, 1902.

6. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behavior, Life History and Surgical End Results, Springfield, Ill., Charles C Thomas, Publisher, 1938.

7. Verhoeff, F. H.: Tumors of the Optic Nerve, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1027.

8. Pagenstecher, A.: Ueber Opticustumoren, Arch. f. Ophth. **54**:300, 1902.

9. Dusaussay: Sarcome angiolithique du nerf optique gauche, Bull. Soc. anat. de Paris **10**:211, 1875.

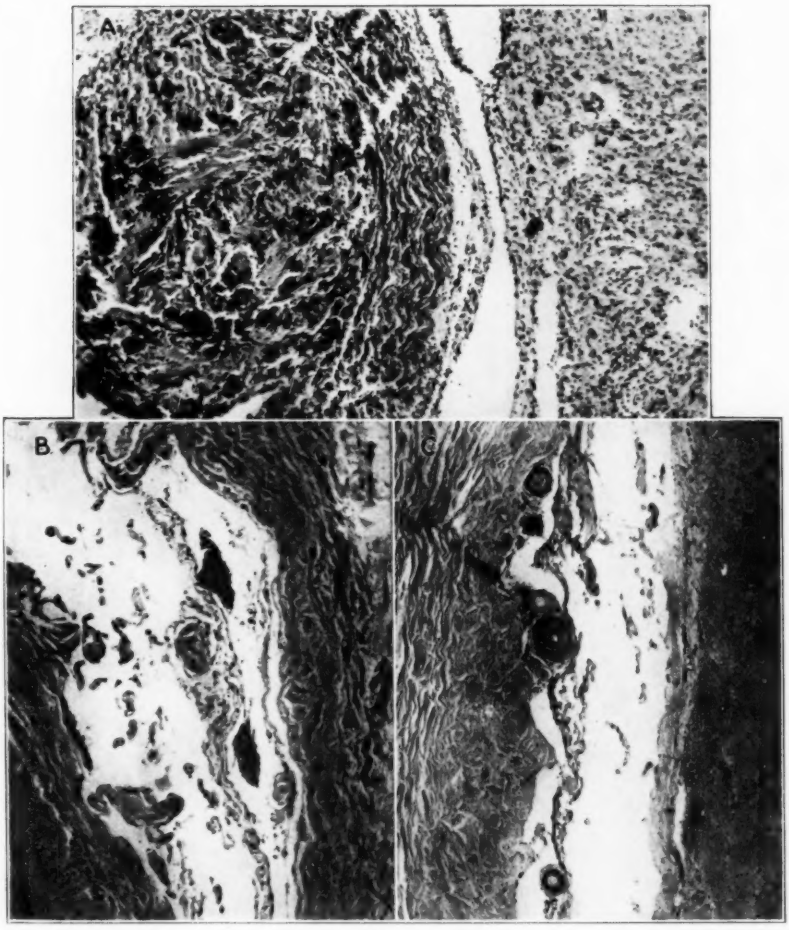

Fig. 12.—(*A*) Neurofibroma, with abortive Verocay bodies, serpentine fibers and edema, × 90, A.I.P. neg. no. 104515; (*B*) normal arachnoid cells with cell clusters, × 55, A.I.P. 100539; (*C*) normal optic nerve with psammoma bodies in arachnoid, × 50, A.I.P. neg. no. 100525.

Cases of intraorbital meningioma without involvement of the optic nerve sheath were reported by de Schweinitz[10] (1914), Bailey[11]

10. de Schweinitz, G. E.: Psammosarcoma of the Orbit in a Girl of Thirteen: Successful Removal with Preservation of the Eyeball and Its Functions, Tr. Am. Ophth. Soc. **13**:617, 1914.

11. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1933.

(1933), Love[12] (1935) and Aebli[13] (1945). Such lesions are, of course, primary in the cranium, generally arising in the olfactory groove or the sphenoidal ridge and extending into the orbit through the dura and bone.

Cushing and Eisenhardt described a case, reported to them by Friedenwald, which was thought to demonstrate conclusively, on the basis of the presence of a normal optic nerve sheath central to the tumor and of roentgenologic evidence indicating integrity of bone, that primary meningiomas of the optic nerve sheath do occur.

It is clear, then, that intraorbital meningioma may occur with or without an intracranial meningioma; if both the orbit and the cranial cavity contain tumors, either may be the primary site. If there is any evidence that the tumor is not confined to the orbital cavity, craniotomy is mandatory.

In this series of 17 cases of meningioma, 40 years was the median age. In 3 patients, or almost 20 per cent, the patient was under 14 years of age. In 12 cases information concerning symptoms was available, and in 9 of these the initial symptom was exophthalmos, which had been present for an average of five years. In 1 case there was a complaint of decreasing vision for three years and of exophthalmos for the last two years, an order of symptoms the reverse of that ordinarily encountered in cases of orbital meningioma. In 2 cases the tumor was incidentally encountered at pathologic examination of the globe after enucleation for the ocular pain of absolute glaucoma secondary to chronic iridocyclitis. In addition to exophthalmos, loss of vision was noted in 3 cases. In 2 instances, diminution of vision accompanied the exophthalmos, and in the third it had been noted only six months, although proptosis had been present for several years. Exophthalmos, then, was recorded in a total of 10 cases; its absence was noted in 2 cases, and there was no pertinent statement in 5 cases.

In 2 cases there was swelling of the lids. Chemosis was noted in 3 cases. A clinically palpable mass was observed in 1 case, a finding which is, of course, unusual with the posteriorly situated meningioma. Specific mention of abnormal ocular movements was made in only 3 cases. There were limitation of external rotation in 2 cases and total immobility in another, in which the tumor filled the orbit. In 9 cases the location of the meningioma was described. In 4 it surrounded the nerve; in 1 it filled the orbit; in 3 it was in the outer portion of the orbit, and in 1 it was noted superiorly.

12. Love, J. G.: Transcranial Removal of an Intraorbital Meningioma, Proc. Staff Meet., Mayo Clin. **10**:213, 1935.

13. Aebli, R.: Meningioma of the Sphenoidal Ridge: Report of a Case, Arch. Ophth. **33**:86 (Jan.) 1945.

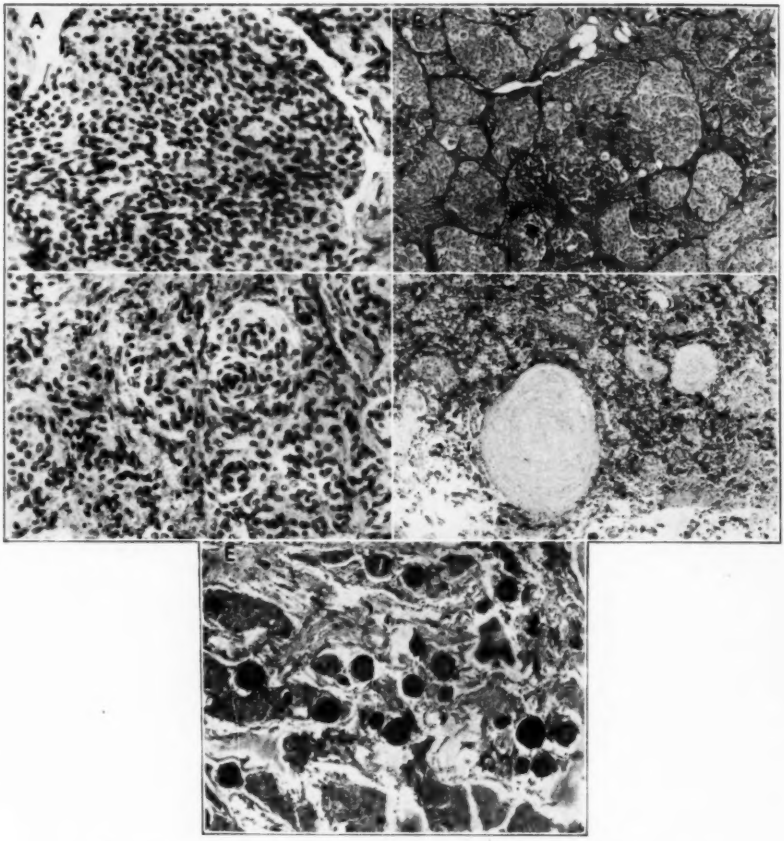

Fig. 13.—Meningioma. (*A*) Meningothelial type, × 285, A.I.P. neg. no. 100536; (*B*) alveolar type, × 50, A.I.P. neg. no. 100533; (*C*) cellular whorls, × 285, A.I.P. neg. no. 100537; (*D*) early psammoma bodies, × 55, A.I.P. neg. no. 100538; (*E*) calcifying psammoma bodies, × 55, A.I.P. neg. no. 100524.

Histologically, the meningiomas were of four types. The first, or meningothelial type, of which there were 2 specimens, was characterized by syncytial sheets of cells, uniformly distributed (fig. 13 *A*). Oval to round, vesicular nuclei were noted, which contained moderate amounts of chromatin and an occasional dark-staining nucleolus. The cells had scarcely distinguishable boundaries but appeared to be uniform in size and shape. An occasional nucleus was represented only by a shell from

which the central nuclear substance had been lost. Mitotic figures were rare, and there was no hyperchromatism. The second type, represented by 8 specimens, differed from the meningothelial type only in the alveolar grouping of the cells within delicate fibrous stroma (fig. 13 *B*). In the third type, represented by 6 specimens, the cellular arrangement was less orderly, and psammoma bodies and whorls were prominent. In figure 13, *C* shows the whorls; *D*, the early hyalin masses, with a few nuclei yet remaining, and *E*, the fully developed psammoma bodies.

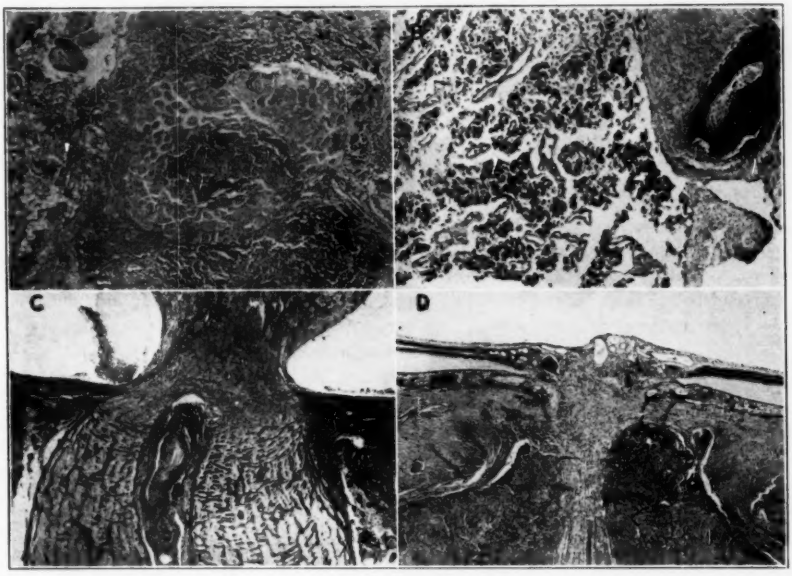

Fig. 14.—Meningioma. (*A*) Bone proliferation and/or invasion, × 75, A.I.P. neg. no. 100535; (*B*) infiltration of extraocular muscle, × 50, A.I.P. neg. no. 100532; (*C*) extension along central vessels in optic nerve, × 15, A.I.P. neg. no. 100529; (*D*) invasion of nerve head (Coston, A. O.: Primary Tumor of Optic Nerve, with Report of Case, Arch. Ophth. **15**:696 [April] 1936), × 20, A.I.P. neg. no. 100540.

In the 1 specimen of the fourth type, the cells were more epithelioid and robust; strands of cells were separated by thin-walled vascular channels, a feature not noted in the other specimens.

In no instance was there microscopic evidence of a fibrous capsule; the tumors were, in general, locally invasive. The neoplasm often infiltrated orbital fat, and in 1 case the presence of bone and periosteum indicated probable infiltration of the orbital wall, with associated osseous

hyperplasia (fig. 14 *A*). Voluntary muscle was invaded in several specimens (fig. 14 *B*). In 1 instance the tumor extended along the central retinal vessels within the optic nerve (fig. 14 *C*). In 1 case the tumor invaded the retina at the disk (fig. 14 *D*).

In 6 of the 8 cases in which roentgenographic studies were made, no abnormalities were observed; in 1 case thickening of the external wall was noted, which at operation was characterized as osteomatous. In this case a radiopaque, soft tissue mass was reported. In this specimen, no psammoma bodies were observed in the sections examined. Psammoma bodies were noted in great numbers in 1 case and were sparsely distributed in another of the 6 cases in which roentgenologic examination was reported as showing nothing abnormal. The presence of psammoma bodies in random microscopic sections does not correlate with radiopacity, although it is assumed that heavy depositions of calcium would be apparent roentgenographically. The roentgenogram did not reveal the moderate orbital erosion which was observed at operation in 1 case.

In 11 of the 12 cases of meningioma in which operation was described, the procedure was enucleation with excision of the tumor. In 1 of these cases, because of the subsequent onset of marked swelling of orbital soft tissue, the orbit was exenterated and a large amount of tumor tissue was removed. In a second case, a small intracranial mass was noted five years after enucleation at a second operation by a neurosurgeon. In only 1 of the 12 cases was the Krönlein operation performed. The tumor was described as having been entirely within the orbit, but five months after operation there were total blindness and intense swelling of the lid. An osteoplastic craniotomy was performed, disclosing a meningioma of the anterior and middle fossae.

In 9 cases there was no evidence of recurrence at intervals ranging from six months to twenty-one years after operation. In only 1 of the 2 cases in which an intracranial lesion was demonstrated were follow-up data available. In this instance the patient was well eight years after the original operation and three years after craniotomy. The delayed discovery of the intracranial tumor apparently did not vitiate the possibility of an eventual favorable result. No follow-up data were available in 7 cases. One of the cases in which the existence of intracranial tumor was established by operation was among the 3 in which preoperative irradiation was given.

In summary, tumors of the meninges observed within the orbit occurred in patients representing a broad age distribution, from 8 to 83 years. The patients usually noted slowly progressive exophthalmos with gradual loss of vision. On the basis of the cases studied, it appears that enucleation with excision of the tumor may be adequate, and that

if intracranial tumor is later noted it may be successfully removed. Primary transcranial approach would, of course, expose an associated intracranial tumor. In cases in which more conservative surgical procedures on the orbit are contemplated, roentgenologic, pathologic and functional studies become even more important in ruling out tumors within the calvaria.

Glioma.—Five of the orbital tumors were a result of enlargement of the optic nerve in which the increase in size was due primarily to neoplastic proliferation of the supporting tissue of the nerve, the glial network.

A patient 15 years of age was the only one with glioma of the optic nerve occurring beyond the first decade of life. In all cases exophthalmos was the presenting symptom, with a duration of from two to four years. Decrease in vision was invariably noted, but in the 2 instances in which its duration was indicated it had made its appearance more recently than the proptosis.

Although there is similarity between the symptoms of glioma and those of meningioma, the age of the patient will usually serve as a distinguishing factor. No rigid criterion can be enunciated, but in general it may be accepted that the older the patient the greater the probability that the tumor is a meningioma.

Grossly, the tumors were described as from the size of a cherry to that of a walnut. Microscopically, attenuated connective tissue septums separated bundles of nerve tissue in which the glial element, particularly astrocytes, had proliferated (fig. 15 *A*). In the nerve adjacent to the pronounced tumefaction, similar hyperplastic changes of milder degree were present. Verhoeff [14] described a peculiar arachnoidal proliferation which suggests primary meningioma (fig. 15 *B*). The swelling did not extend to the optic papilla in any of the cases in this group.

In all cases treatment was by enucleation with excision of the tumor. Significant follow-up information was available in only 1 case; the patient was well five years after operation. Verhoeff [14] indicated that incomplete excision of these tumors has resulted in regression of the remaining mass, so that complete excision may be less important than in the case of the meningioma, the other intraorbital tumor, with which intracranial lesions may coexist. In at least 1 case the tumor was noted to extend through the optic foramen.

Neurofibrosarcoma.—Nine tumors were comprised of spindle-shaped cells which were producing collagen. In spite of varying degrees of anaplasia, moderate palisading and fasciculation (fig. 15 *C*) were dis-

14. Verhoeff, F. H.: Primary Intraneural Tumor of the Optic Nerve, Arch Ophth. **51**:239, 1922.

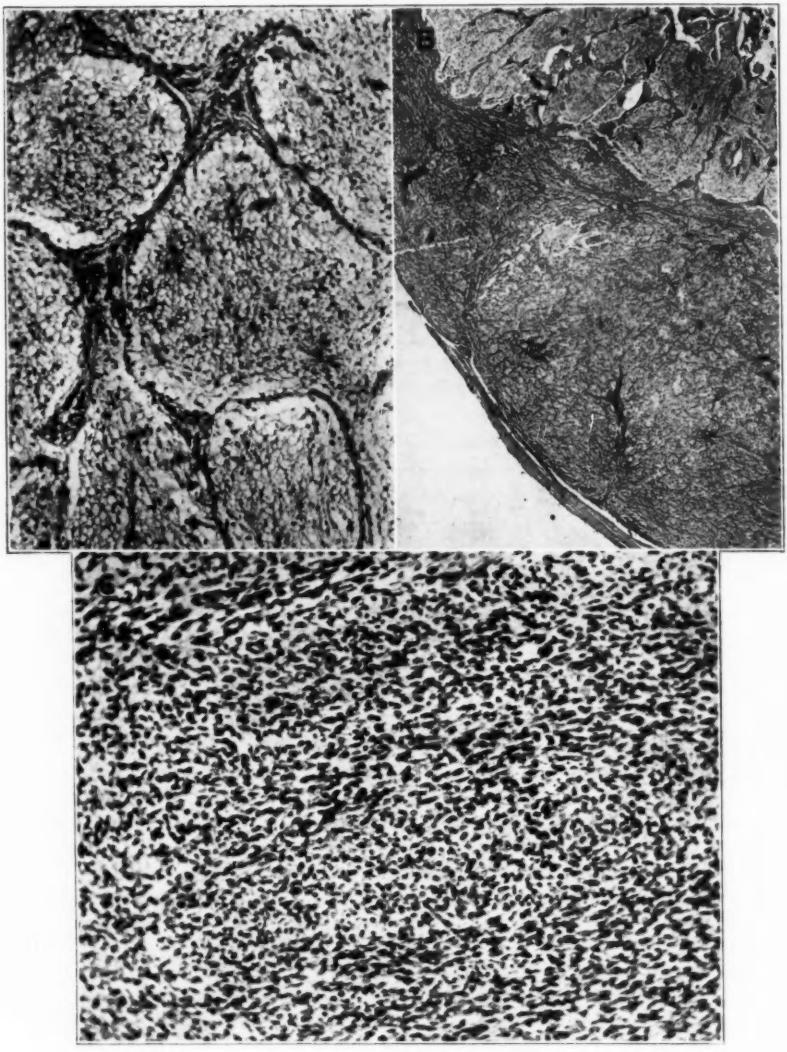

Fig. 15.—(*A-B*) Glioma of optic nerve. (*A*) Thickened nerve bundles, × 90, A.I.P. neg. no. 101312; (*B*) associated arachnoidal proliferation, × 17, A.I.P. neg. no. 101314; (*C*) neurogenic fibrosarcoma with fasciculation of cells, × 210, A.I.P. neg. no. 104517.

tinguishable; this cellular disposition suggested that the tumor was related to nerve and probably arose in the nerve sheath, or so-called perineural connective tissue.

The age of the patients varied from 4 to 71 years, and there was not the preponderance of young patients noted in the group of mesenchymal sarcomas. Follow-up data were available in 6 cases. Two patients were alive and well two and four years, respectively, after operation. Two other patients were alive ten months and five years after operation, but recurrence had been noted clinically at ten months and three years, respectively. The 2 recorded deaths occurred one and two years after operation, the first with at least local evidence of recurrence and the second with evidence of metastasis to the lung. It would appear that the prognosis of neurogenic sarcoma is not different from that of other malignant tumors originating in mesenchymal tissue.

DEVELOPMENTAL FAULTS

Eighteen tumors in this series originated in developmental abnormalities; 17 were dermoid cysts and 1 was a teratoma. Both these neoplasms are regarded as congenital and as resulting from the inclusion of dermoid tissues along the lines of embryonic fissure. In spite of the congenital nature of these tumors, symptoms often do not appear for several years, and probably result from episodes of increased growth and secretory activity of the lining cells. Presenting symptoms in the present series were related to a "mass in the orbit" and varied in duration from five months to over twenty years. The average age was 22 years, the extremes being 17 months and 46 years. In only 2 infants and 3 adolescents had the masses been noted from birth.

In all but 1 case, the lesion presented anteriorly and was simply excised. In the exceptional case, a woman aged 46 had exophthalmos of three years' duration, associated with decreasing vision. The dermoid and an osteoma of the external wall of the orbit were removed by the Krönlein operation.

The dermoids were cystic masses with cavities measuring as much as 2 cm. in diameter. They were usually filled with a pultaceous material, comprised of fatty, keratic debris containing hair fibers (fig. 16 *A*). The cavities were lined by squamous epithelium with a surrounding connective tissue stroma, through which the appendages of the skin reached the cyst (fig. 16 *B*). The thick squamous cell lining had often been destroyed, probably by pressure and repeated inflammation, and the walls had become hyalinized (fig. 16 *C*). Cellular reaction to the lipids included lipidic histiocytes and epithelioid and giant cells. Calcific deposits were present in some areas. The thickness of the wall varied from several millimeters to a fraction of a millimeter, the

thin wall accounting for difficulty in removing several of the dermoids without rupture.

The surrounding connective tissue was often vascular and contained numbers of plasma cells and lymphocytes. The inclusions of orbital

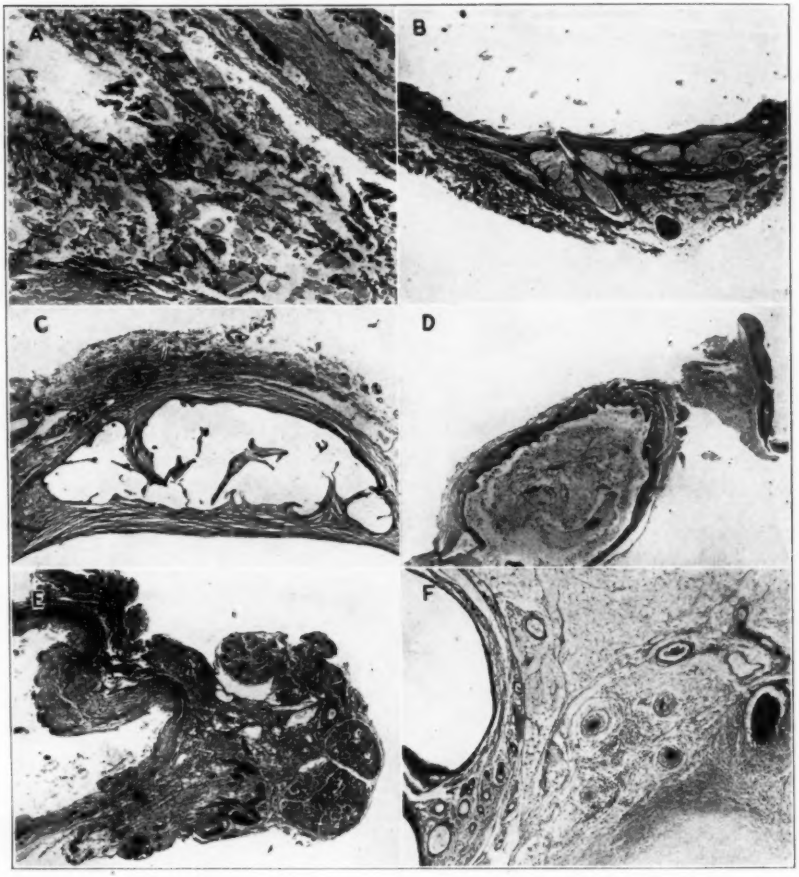

Fig. 16.—Dermoid cyst. (*A*) Hair shafts and keratic debris, × 55, A.I.P. neg. no. 100526; (*B*) hair follicle, sebaceous glands and calcium deposits, × 15, A.I.P. neg. no. 100528; (*C*) multilocular cyst with hyalinized lining, × 10, A.I.P. neg. no. 100530; (*D*) adherent periosteum and bone, × 15, A.I.P. neg. no. 100532; (*E*) proximity to lacrimal gland, × 15, A.I.P. neg. no. 100527; (*F*) teratoid tumor containing epithelial cysts, hair shafts and cartilage, × 40, A.I.P. neg. no. 101313.

nerve and muscle in many sections indicated the difficulty of dissecting even the innocuous dermoid from the orbit without at least minor destruction. Many locules were observed in a specimen (fig. 16 *C*) taken from a boxer, whose orbit had been exposed to repeated trauma. Gifford [15] commented on the extensive ramification of some dermoids, making extirpation difficult and accounting for the frequency of recurrence. In at least 5 of the cases in this group there had been a previous operation, but in only 1 was it recorded as excision of the mass. In 1 instance at least the cyst was attached to periosteum (fig. 16 *D*), and the surgeon removed adjacent bone, which grossly appeared to have been involved. Stout [16] stated that intraorbital dermoids may erode outward and that dermoid cysts of the skull and facial bones may erode into the orbit. None in this series was of that nature. In 1 instance a portion of lacrimal gland to which the cyst adhered was removed with it (fig. 16 *E*). The presence of cartilage, in addition to the dermoid elements, in 1 specimen led to a pathologic diagnosis of teratoma (fig. 16 *F*).

SECONDARY TUMORS

The 38 tumors which were secondary in the extraocular orbit were of five histologic types.

Carcinoma.—Twenty-four tumors were malignant epithelial growths arising outside the orbit. The average age of the patients was 58 years. Exophthalmos was a presenting complaint in 6 cases and was noted with primary tumor of the breast in 3 cases, with squamous cell carcinoma, probably arising from the sinuses, in 2 cases, and with conjunctival carcinoma in 1 case. In the last case the tumor had arisen in the superior fornix, but apparently its extension into the orbit was more rapid than the growth of the primary tumor. The presence of an anteriorly situated mass was the initial complaint in 8 cases, including 5 cases in which the primary tumor was in the adjacent skin, 1 case in which it was in the conjunctiva, 1 case in which it was in the nasolacrimal duct and 1 case in which it was metastatic from the large intestine. Loss of vision was noted in 1 case and was related to an associated tumor in the maxillary sinus.

In 17 cases the tumor had invaded the orbit from an adjacent site; it resulted from hematogenous dissemination in 4 cases, and the origin was not established in 3 cases. Of the locally arising tumors, a squamous cell carcinoma had invaded the orbit from the adjacent nasal sinuses in 5 cases (from the antrum in 3 and from the ethmoid cells in 2 cases). The origin of an orbital adenocarcinoma was suggested by

15. Gifford, H.: Recurrent Dermoid Cyst: Successful Treatment with Trichloroacetic Acid, Arch. Ophth. **2**:305 (Sept.) 1929.

16. Stout, A. P.: Human Cancer, Philadelphia, Lea & Febiger, 1932.

roentgenologic examination to have been the maxillary sinus. A squamous cell carcinoma had invaded the orbit from the surrounding skin in 1 case, and a basal cell carcinoma, in 4 cases. The lacrimal sac and the nasolacrimal duct contributed an adenocarcinoma and squamous cell carcinoma, respectively (fig. 17 *A*). Squamous cell carcinoma had arisen in the conjunctiva in 2 cases; the site was not stated in 2 others, but it is likely that they were local. The metastatic orbital masses were primary in the female breast in 3 cases and in the colon in 1 case. A glandular carcinoma and 2 undifferentiated carcinomas were

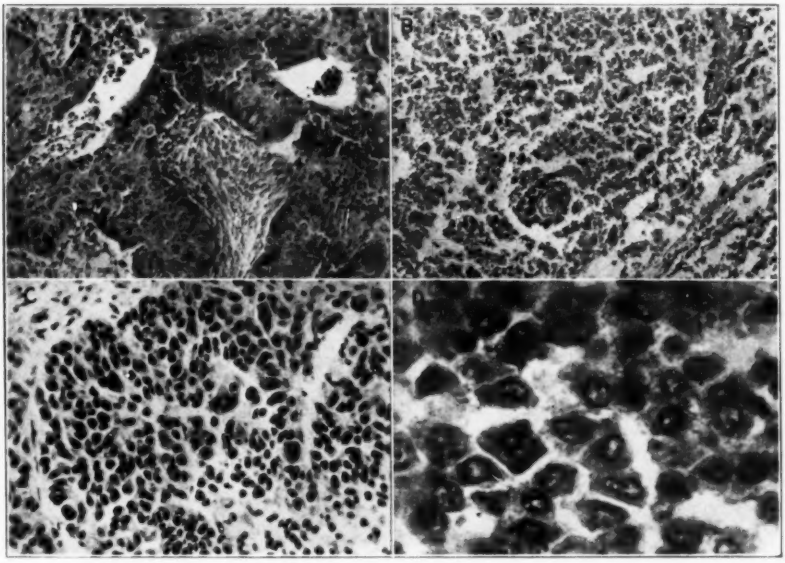

Fig. 17.—Secondary orbital tumors. (*A*) Squamous cell carcinoma arising in nasolacrimal duct, × 160, A.I.P. neg. no. 101315; (*B*) metastatic neuroblastoma, showing perivascular cuffs of cells, × 98, A.I.P. neg. no. 101316; (*C*) malignant melanoma, × 317, A.I.P. neg. no. 101317; (*D*) pituitary adenoma, × 1,000, A.I.P. neg. no. 102437.

of undetermined origin. In 1 case widespread metastases were already present at the time of operation; in a second, the tumor in the breast was discovered only after the orbital mass had been removed by the Krönlein operation. Similar information was not available concerning the other case.

The tumor metastatic from the colon was situated anteriorly in the orbit and was adherent to the periosteum of the superior orbital

wall. Its probable origin in the gastrointestinal tract was suggested by its microscopic appearance before the discovery of the primary tumor.

All the 15 replies to follow-up inquiries reported the death of the patient. The 12 deaths from tumor in from four months to three years indicated the intrinsic severity of tumors which extended or metastasized, and the 3 deaths from other causes were related to the age of patients with carcinoma.

Neuroblastoma.—The ages in the 6 cases of intraorbital neuroblastoma ranged from 2 months to 13 years. In one-half the cases exophthalmos was the presenting symptom and had been noted from five to sixteen months. In the other 3 instances the lesions were anteriorly situated and had been present for periods of three to nine weeks.

The postoperative interval was sufficiently great to warrant follow-up investigation in only 3 of the cases. In 1 of these, the patient was alive one year after exenteration, but there was evidence of local recurrence and of an intracranial lesion. Autopsy in the other 2 cases revealed a primary tumor in only 1, and in that case it occurred in the adrenal gland. In the other case it was assumed that a retroperitoneal or other paravertebral sympathetic ganglion was the parent focus.

The differentiation of this tumor histologically (fig. 17 *B*) from other morphologically similar neurogenic tumors, e. g., the retinoblastoma, is often difficult, and the ophthalmologist's statement that intraocular tumor is not present is important. The diagnosis can be considered conclusive only when the primary tumor is found.

Malignant Melanoma.—The large numbers of epibulbar extensions of choroidal tumors having been excluded from consideration, 6 cases of intraorbital malignant melanoma remain. In 4 of these cases the tumor contained no pigment in the sections examined and was cytologically of the type which in the choroid would be classified as epithelioid (fig. 17 *C*). In 1 of the cases the initial complaint had been that of an enlarged inguinal lymph node, and by the time of enucleation there was generalized lymphadenopathy. Pathologic examination of the ipsilateral eye revealed no intraocular tumor. The eyes in the other 3 cases were not available for inspection.

The fifth case was one of a pigmented tumor which would be classified as a mixed cell type. Autopsy revealed extensive generalized metastases, but both eyes were free of tumor. The grossly suspicious lesions of the skin proved histologically to be benign. No other possible primary source was found. Only in the sixth case was the orbital mass related to an intraocular melanoma, for which enucleation had been performed seven months previously.

Retinoblastoma.—One tumor was a retinoblastoma recurrent from an intraocular growth for which there had been enucleation eleven months prior to onset of swelling of the lid and appearance of the orbital mass. Cytologically, the tumor was identical with the usual intraocular neoplasm.

Adenoma of the Pituitary Gland.—The records indicated that a clinical diagnosis of suprasellar meningioma had been made in 1 case; the history was of fourteen years' duration. Microscopic examination of the specimen removed from the orbit revealed sheets of epithelial-like cells characteristic of the eosinophilic adenoma of the anterior lobe of the pituitary (fig. 17 *D*).

SUMMARY

A series of 222 cases of intraorbital tumor from the Registry of Ophthalmic Pathology were studied with particular attention to the histologic characteristics, but also with regard to clinical features. One hundred and eighty-four of the tumors were primary in the orbit; these included 93 of mesenchymal origin, 48 related to the nervous system, 25 mixed tumors of the lacrimal gland and 18 dermoids. Forty-four, or 24 per cent, of the primary tumors were malignant. Thirty-eight of the tumors examined were secondary in the orbit and included 24 carcinomas, 6 neuroblastomas, 6 malignant melanomas, 1 retinoblastoma and 1 adenoma.

Certain clinical features appeared to be characteristic of various classes of tumors. Lipomas and dermoids were often anteriorly situated in the orbit, while sarcomas, meningiomas, neurofibromas and gliomas were more frequently posterior and caused exophthalmos. Mixed tumors and hemangiomas were about equally divided between the two locations, approximately half of each causing exophthalmos.

Malignant mesodermal tumors, gliomas of the optic nerve, hemangiomas and metastatic neuroblastomas occurred predominantly in youth. The tumors of the hematopoietic system and secondary carcinomas were ordinarily concomitants of more advanced age. The age distributions of other types of tumor were less characteristic.

Among the histologically benign tumors, recurrence was most frequent in the mixed tumors and the hemangiomas because of the difficulty of removal; remnants of the tumor are often left behind and form the nucleus for continued growth.

In general, the data gathered from the 222 cases in this series are in agreement with those of other authors and support accepted views regarding treatment and prognosis in most categories.

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ABSTRACT OF DISCUSSION

DR. GEORGIANA DVORAK-THEOBALD, Oak Park, Ill.: As Dr. Forrest has pointed out, correlation of clinical data with histologic features is of particular importance in the case of orbital tumors, since, more than is true of most ophthalmic disease, the treatment and prognosis are determined by microscopic changes. Moreover, it seems that the textbooks and encyclopedias present the material on orbital tumors in a much more hit-or-miss manner than that on other pathologic states; hence, we are particularly indebted to Dr. Forrest for his clearcut classification of these tumors according to their origin in the various types of orbital tissue. It is of particular importance that there be a good basic classification now that the literature on these tumors is increasing rather rapidly, and there should be some consistency of nomenclature. With increased standardization of terminology, there will, perhaps, be less variation in reported incidence of the various types than is true now. A check of the articles by Benedict and others and a visit to Dr. Ingall's exhibit in the present Session will make clear the rather wide differences in terminology.

DR. T. E. SANDERS, St. Louis: Of the intraocular tumors, over 90 per cent are either the malignant melanoma of the uvea, a tumor of adults, or the retinoblastoma of infants. The problem of the intraorbital tumor is quite different. The exact nature of the tumor is not known until microscopic examination is made.

Lesions anterior to the orbital fascia are better coiisidered to be in the lid. They present as superficial, palpable masses, without exophthaimos, and can be easily removed through a simple incision in the lid. The 17 dermoid cysts in this series would seem to be in this class. The author states that the majority of the 19 lipomas were situated anteriorly, presenting as a mass, and that the tumor was histologically indistinguishable from normal orbital fat. I believe that many of these lipomas were really a herniation of orbital fat through a small defect in the orbital septum, and were not neoplastic.

I agree with Dr. Forrest that the acurate diagnosis and classification of a tumor of the hematopoietic system is extremely difficult. Some of the lymphomas, better called lymphocytomas, are local tumors. However, the majority are associated with such systemic diseases as lymphosarcoma, leukemia and Hodgkin's disease, and thus should be considered a local manifestation of a general condition. The meningioma should also be considered a secondary tumor, as the majority of the 17 meningiomas in this series almost surely invaded the orbit from a lesion primarily intracranial.

I was interested in Dr. Forrest's group of mixed tumors of the lacrimal gland as it was exactly ten years ago, before this section (Mixed Tumors of the Lacrimal Glands, ARCH. OPHTH. **21**:239 [Feb.] 1939; *Tr. Sect. Ophth., A. M. A.*, 1938, p. 214) that I reported a series of these cases. The present results again show that these tumors have an extremely high rate of recurrence, tend to be invasive and are potentially fatal. Therefore, I believe they cannot be considered benign.

It is not often that the opportunity arises to collect such a large and representative series of intraorbital tumors. The present series is particularly important, as adequate clinical data and the results of careful pathologic study are available. The data presented by Dr. Forrest are of value in several ways. His tabulation presents the types of tumors arising in the orbital tissues, with their relative frequency in this series. He has also correlated the variable clinical symptoms with the histologic picture. This knowledge will provide a much better idea of the pathologic possibilities in a particular case. The relatively large number of cases in this

series in which final clinical results were known gives a clearer understanding of the prognosis of these tumors.

The orbital tumors remain a real clinical problem. Although the symptoms are usually characteristic, the diagnosis of the presence of a tumor in the orbit is at times difficult. In my experience, roentgenograms often do not show bony defects in the orbit, and, thus invasive tumors are not recognized as such before operation.

DR. ALAN C. WOODS, Baltimore: How does Dr. Forrest classify the ordinary pseudotumor, by whatever name he chooses to call it? Dr. Walter Dandy found that about 20 per cent of his large series of tumors were lesions of Christian-Schüller disease. I was rather surprised at the absence of this entity in the present series.

DR. ARNOLD W. FORREST, New York: There can be no doubt as to the anatomic anterior limit of the orbit, but, as pathologists, we were all, of course, entirely dependent on the clinicians' description of where the tumors lay. The question whether the lipomas were true tumors or herniations had to be considered, but we could do no more than accept the clinicians' word for the fact that the tumors lay within the orbit.

The question of the lymphoma is an extremely interesting one. Dr. Sanders comments that it should be considered part of the generalized disease rather than as an isolated lesion. Schulz and Heath (*Radiology* **50**:500-505 [April] 1948) pointed out that the lymphoma of the obrit is more commonly an isolated lesion and does not carry the grave implications of lymphomas elsewhere. I believe that the experience of Dr. Hayes Martin, at Memorial Hospital in New York, substantiates the statement that lymphomas in the head and neck in general are different from lymphomas elsewhere and do not carry the grave prognosis of such lesions. We did follow the patients; and, although 2 showed evidence of leukemia and 2 others signs of generalized disease within a year, 4 or 5 of them were well after as long as five and ten years. Meningioma, often a primary tumor, might in other cases be secondary to meningioma within the skull.

Dr. Woods's observation that cases of pseudocellular tumors and of Christian-Schüller disease are absent from this series is a valid remark from the clinical point of view, but from the standpoint of the pathologist it seemed wise to exclude them as representing inflammation rather than neoplasm.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Comparative Ophthalmology

HEREDITARY APLASIA OF THE OPTIC NERVE IN THE MOUSE. HUGO J. BEIN, Ophthalmologica **113:** 12 (Jan.) 1947.

Aplasia of the optic nerve was found in a number of animals in the "Basil waltzing mouse stock." The eyes were normal externally. This deformity was found to be hereditary and was frequently combined with a misshapen skeleton. It was found possible to continue to breed mice with optic aplasia.

F. H. ADLER.

Cornea and Sclera

CEPHALOSPORIUM KERATITIS. A. J. BEDELL, Am. J. Ophth. **30:** 997 (Aug.) 1947.

Bedell reports a case of corneal ulcer resulting from injury by a cow's tail. The clinical picture was so suggestive of a mold as the cause of the ulcer that potassium iodide was given, and satisfactory regression resulted. Subsequent investigation proved that the cause was the extremely rare Cephalosporium species.

W. S. REESE.

TREATMENT OF PERFORATED CORNEAL ULCER BY AUTOPLASTIC SCLERAL TRANPLANTATION. S. LARSSON, Brit. J. Ophth. **32:** 54 (Jan.) 1948.

In connection with an operation for retrobulbar hemangioma, a 7 year old girl had lagophthalmic corneal ulcer, which developed into a descemetocele. Four attempts elsewhere to close the ulcer with a conjunctival flap did not lead to the desired result. The wound became larger, and there was danger of perforation. A scleral disk was punched out of the same eye and transplanted into the wound, after the edges of the latter had been excised. The graft was covered with conjunctiva. The result was good: The transplant fitted in comfortably, the ulcer closed, and vision was comparatively good.

W. ZENTMAYER.

THE SURGICAL TREATMENT OF PTERYGIUM. A. D'OMBRAIN, Brit. J. Ophth. **33:** 65 (Feb.) 1948.

D'Ombrain considers that pinguecula and pterygium are fundamentally identical, etiologically and structurally, that the primary focus of activity is in the connective tissue and that efficient surgical treatment of pterygium must include removal of this tissue. After the pterygium is freed, its apex is grasped at its tip with fixation forceps and held up vertically and taut by an assistant. With fine forceps and sharp-pointed scissors, the whole subconjunctival portion of the pterygium, from the under surface of the epithelial layer as far medially as the plica semilunaris, is dissected off. This comes away in one triangular piece, and is a remarkably thick and extensive structure underlying the whole extent of the pterygium; indeed, it is the pterygium. A sliver of the

free edge of the remaining conjunctiva is excised, leaving a bare strip of sclera several millimeters in width. The conjunctiva rapidly grows over the scleral strip, but not before the corneal surface has healed.

W. ZENTMAYER.

Experimental Pathology

SOME RESEARCHES ON THE RESPIRATION OF THE CORNEA IN ALBINO RATS. A. BAKKER, Brit. J. Ophth. **31:** 100 (Feb.) 1947.

Bakker gives the following summary of experiments which had as their object the study of the influence of various concentrations of carbon dioxide and the absence of oxygen in the surrounding atmosphere on the cornea of anesthetized albino rats. With the help of artificial breathing, it was possible to close up the animals in a tank filled with one kind of gas or another, and in this way to expose the eyes of the experimental animals under otherwise normal conditions to the gas under investigation. As a result of these experiments, Bakker is of the opinion that carbon dioxide is able to penetrate through the cornea from the surrounding atmosphere to the anterior chamber. It could be determined that the so-called selective penetration of carbon dioxide through the cornea is not probable. Absence of oxygen in the surrounding atmosphere does not inhibit the normal life of the cornea. The corneas remained transparent for many hours in an atmosphere of 8 per cent carbon dioxide and 92 per cent nitrogen. Special attention was paid to possible pathologic changes in the corneas after the experiments were concluded.

The article is illustrated.

W. ZENTMAYER.

EXPERIMENTAL HYPERTENSIVE RETINOPATHY. N. BELMONTE GONZALEZ, Arch. Soc. oftal. hispano-am. **7:** 214 (March) 1947.

The author, having made observations on the fundus oculi in dogs subjected to experimental hypertension, came to the following conclusions: 1. Experimental nephrogenic chronic arterial hypertension in the dog in the end produces changes in the fundus similar to those occurring in man with hypertensive vascular sclerosis. 2. The retention metabolites brought about by total renal nisufficiency after bilateral nephrectomy do not give rise to any retinal changes, for the same reason that they do not produce an increase in arterial tension. 3. Ligation of both ureters in the dog creates pathophysiologic conditions in the ocular fundus which bring about angiospastic retinitis.

The article is illustrated.

H. F. CARRASQUILLO.

General

STEVENS-JOHNSON SYNDROME. D. O. WRIGHT, E. M. GOLD and G. JENNINGS, Arch. Int. Med. **79:** 510 (May) 1947.

Wright and his associates point out that the syndrome described by Stevens and Johnson in 1922 was designated as a "new" eruptive fever associated with stomatitis, ophthalmia, cutaneous eruption and constitutional symptoms. The syndrome deserves emphasis because tragic complication involving the eyes, consisting of corneal ulceration or

panophthalmitis, with partial or complete loss of vision, have been frequent. These severe complications of the eyes did not occur in 9 patients treated by the authors with sulfonamide compounds and/or penicillin. Five patients were treated with sulfonamide drugs and 4 patients with penicillin systemically or topically or both. Complete recovery without sequelae occurred in all but 1 patient, who had mild conjunctivitis with slight symblepharon, but no corneal involvement. Enthusiasm for any type of therapy in this syndrome must be tempered by recognition of the fact that the severity of the clinical course varies greatly and that recovery without ocular complications is not uncommon. In 6 of the 9 cases at least one previous attack was experienced without permanent ocular damage.

W. ZENTMAYER.

General Diseases

CORNEAL LESIONS IN HODGKIN'S DISEASE. P. MATTEUCCI, Am. J. Ophth. **30:** 136 (Feb.) 1947.

Matteucci reports a case of Hodgkin's disease in which a bilateral herpetic type of keratitis appeared. He notes the rarity of this complication, the effect of radium therapy on the ocular condition, confirming the sensitivity of specific cells of malignant lymphogranuloma to radium, and the probable etiologic association between the supposed virus of lymphogranuloma and the corneal lesions.

W. S. REESE.

OCULAR MANIFESTATIONS OF MUMPS. J. FIELDS, Am. J. Ophth. **30:** 591 (May) 1947.

Fields reports a case of keratitis due to mumps; he describes the condition as a definite clinical entity and suggests the term "mumps keratitis."

W. S. REESE.

OCULAR CHANGES IN ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS. F. C. CORDES and S. D. AIKEN, Am. J. Ophth. **30:** 1541 (Dec.) 1947.

Cordes and Aiken report a case of acute disseminated lupus erythematosus with autopsy. They conclude from the study of this case and a review of the literature that there is no pathognomonic ocular lesion or combination of lesions in this disease, but that the so-called toxic retinitis is probably the most typical and frequent pathologic change.

W. S. REESE.

OCULAR EXPRESSIONS OF DIABETES. I GIVNER, New York Med. **3:** 5 (March 5) 1947.

Givner reviews the literature on ocular manifestations of diabetes. A survey of 127 patients with juvenile diabetes showed 3 patients, aged 12, 15 and 15, who had had diabetes eight, eleven and nine years, respectively. Each showed pinpoint hemorrhages and venous dilatations, with no arterial changes. In no case were exudates seen which suggested that hemorrhages precede the appearance of the waxy exudate.

A rare observation was made on a patient with phlebosclerosis associated with diabetes of seventeen years' duration in that the aqueous vein showed phlebosclerosis.

W. ZENTMAYER.

XANTHELASMA. AND AUTONOMIC NERVOUS SYSTEM: A NEW SYNDROME. A. BAKKER, Brit. J. Ophth. **31**: 686 (Nov.) 1947.

Bakker gives the following summary: Almost without exception, patients with xanthelasmas have various kinds of allergic disease; and, if they do not, allergic disorders occur, at any rate, among their relatives. As these benign tumors are probably closely related to the cholesterol metabolism and the latter stands under the regulating influence of the autonomic nervous system, and as, in the last analysis, allergic disorders have much to do with the sympathetic and the parasympathetic nerves, an attempt is made to consider all these apparently heterogeneous diseases from one viewpoint, i. e., as a dysfunction of the vegetative nervous system.

W. ZENTMAYER.

Glaucoma

TECHNIC OF NONPERFORATING CYCLODIATHERMY. L. WEEKERS and R. WEEKERS, Ann. d'ocul. **180**: 76 (Feb.) 1947.

In a previous article the authors reviewed the history of this operation. They believe that the effect of the diathermy is to produce an intense vasodilatation of the uveal tract. This is brought about by action on the ciliary nerves, as well as a "biochemical" lesion in the uvea.

They do not think that it is necessary to perforate the sclera in order to obtain the desired effect of lowering the tension. On the basis of their experimental work and their results with patients, they conclude that the most satisfactory position in which to place the electrode is 7 to 8 mm. from the limbus, in the region of the ora serrata. One then gets the maximum vasodilatation, and there is less risk of injuring the lens. They also feel that when this operation is performed the entire ciliary body should be treated. Originally they made eight applications of the diathermy; now they use approximately twenty applications, with a weaker current. The authors feel that the effect of the cyclodiathermy is somewhat analogous to that of multiple cyclodialyses.

The electrode should have a diameter of about 0.75 mm. If one uses a small electrode, the lesion in the ciliary body is more discrete; and since the conjunctiva is not dissected from the globe, there is less conjunctival reaction. The authors employ a pyrometric electrode, which permits an accurate gage of the temperature.

The instrument is described fully. There are two fine wires, one of which carries the current and acts as the first element of the thermocouple. The second wire is the other element of the thermocouple. Each instrument is calibrated before use.

For operation the eye is prepared in the usual manner. Local anesthesia consists of topical application of cocaine and epinephrine, as well as retrobulbar injection. Just prior to operation retrobulbar injection of 1 cc. of 40 per cent ethyl alcohol is given. This is to augment the effect of the anesthetic and to prevent the rise in tension that may occur immediately after the operation. The electrode is applied through the conjunctiva about 8 mm. from the limbus, in the region of the ora serrata. This is so that the nerves to the ciliary body will be affected. The number of applications varies from twelve to twenty. The electrode is held in place for fifteen seconds. The current is raised so that within five seconds the temperature registers

90 C.; this is then maintained for the remaining ten seconds. The eye is not patched after operation.

After the operation, there is moderate chemosis, which lasts for eight to ten days. There is hypesthesia of the cornea, which may be accompanied with roughening of the epithelium. This disappears rapidly. The authors have never seen a case of iritis following the operation. Occasionally, there may be slight mydriasis. There may be a tendency to myopia for a few days. This is ascribed to edema of the ciliary body affecting the zonule of Zinn. There is some edema of the retina in the extreme periphery. This gradually subsides, and one is left with scars, as seen after an operation for disinsertion. They are not enough to interfere with the visual field.

The authors have performed thirty-five operations according to the technic described. The results have equaled those of the perforating cyclodiathermy, and fewer complications have been encountered. They think that cases of chronic glaucoma are the most satisfactory for this type of operation.

The paper concludes with the authors' theory as to the physiologic basis for the operative results.

P. R. McDONALD.

APPRECIATION AND MECHANISM OF THE DESTRUCTIVE EFFECTS PRODUCED BY OCULAR HYPERTENSION. AMADEO NATALE, Arch. d'opht. **7:** 129, 1947.

The author reviews the more recent literature, chiefly the English and American, which has to do with glaucoma. He calls attention to the two types of tension: (1) the dynamic, due to the contents of the sclera, and (2) the static, due to the rigidity of the scleracorneal coat. He discusses intraocular pressure in relation to the cerebrospinal fluid pressure. He refers briefly to the control of the hydrostatic pressure within the eye. He also goes into detail in regard to the pupillary reactions. The close association between the blood and the aqueous humor is taken into consideration. The author points out that he has not tried to make use of all the immense bibliography which he has accumulated. An extensive bibliography is appended.

S. B. MARLOW.

INCOMPLETE GLAUCOMA. ROBERT GERARD, Arch. d'opht. **7:** 511, 1947.

The author presents 5 cases of incomplete glaucoma with studies of the visual fields. He discusses the cupping of the disk, the field defects, the pupillary changes and the changes in the arterial tension of the retina. He concludes that the idea of an incomplete glaucoma is justified. Glaucoma without hypertension is one of the most typical forms of the disease. The pupillary changes, the field defects and the cupping observed without hypertension are characteristic and are to be differentiated from primary atrophy of the optic nerve. He expresses the belief that the cupping in this form of glaucoma is not due to compression of the nerve by intracranial vascular sclerosis.

S. B. MARLOW.

THE EFFECTIVENESS OF A MODIFIED CYCLODIALYSIS. LADISLAUS GAT, Ophthalmologica **114:** 106 (Aug.) 1947.

The author believes that with the Blaskovics-Kettesy modification of cyclodialysis glaucoma can be cured in most cases. The advantages of

the method are the ease of procedure, its adaptability to all forms of glaucoma, the possibility of repetition on the same eye and absence of bad effects when the operation is a failure. The disadvantages are that the intraocular tension is lowered only on the third to fourth day after operation and that there is always the possibility of some bleeding. The author has also noted a postoperative myopia which he believes stops spontaneously after several months. The clinic in which the author works has used this method succesfully in 74.5 per cent of cases of glaucoma.

F. H. ADLER.

Injuries

THE EFFECT OF ALUMINIUM AND ITS ALLOYS ON THE EYE. L. H. SAVIN, Brit. J. Ophth. 31: 449 (Aug.) 1947.

This voluminous report was presented to the Vision Committee of the Medical Research Council. The subject is considered under the following headings: introduction; clinical report of cases of intraocular fragments of the aluminium; alloys; experimental observations on rabbits; illustrative experiments, and histologic changes. The author summarizes as follows:

The literature of intraocular aluminium is reviewed. A case is reported in which a piece of "aluminium zinc" (or possibly zinc base aluminium) was observed over a period of three years as it lay on the retina of an only eye. The metal was at first bright and silvery. Later it became coated with a white cover, probably of aluminium hydroxide. The fragment shifted twice, each time leaving a retinal "imprint," before eventually disintegrating into white powder. In a second case the behavior was similar.

Twenty-five implantations of fragments of aluminium or aluminium alloy were made into the anterior chambers of rabbits by a standardized technic, and 9 implantations were made into the vitreous chamber. There was no clinical difference in the behavior of pure aluminium and that of the various alloys. Doses varying from 0.3 to 20 mg. were used; the ocular reaction tended to be severer with the higher doses.

The fragments were observed to become coated with white powder, with yellowish exudate, with fibrin or, in late cases, with jelly. A late change often seen was powdering and fragmentation of the metallic fragment. In 6 cases the fragment was completely absorbed. Common local changes were necrotic "imprints" left by the metal; of these, 6 imprints were on the cornea, 12 on the iris (9 gray, 2 white, 1 necrotic), 2 in the lens and 4 in the fundus.

Of the general ocular effects on the eye were lenticular opacities, including striae, dots, vacuoles and irregular opacities, in 28 eyes; these opacities were occasionally accompanied with polychromatic luster. The opacities were anterior capsular in 5 eyes, anterior cortical in 6 eyes, posterior cortical in 4 eyes, capsular imprints in 2 eyes and complete cataracts in 3 eyes.

Quiet inflammatory changes in the uveal tract were frequent. These included posterior synechias, 10 cases; iris bombé, 2 cases, and atrophy of the iris, 14 cases. Other changes included pathologic pigmentation of the fundus, in 23 cases; localized choroiditis, in 6 cases, and retinitis proliferans, in 3 cases. Pathologic vascularization, not reported in

the literature in human cases, occurred often in the animals. It is uncertain whether the reaction is specific for aluminium.

Among other oddities were noted bullous keratitis, 2 cases; staphyloma (false buphthalmos), 1 case; zonular keratitis, 2 cases; interstitial keratitis, 1 case; deep keratitis, 1 case; pigmented cornea, 2 cases; pigmented limbus, 1 case, and folds in Descemet's membrane, 2 cases.

Histologic investigations were hampered by technical difficulties. The changes observed were such as would have been expected from the clinical findings. They included hyalinization and vascularization of the cornea, iritis, atrophy of the iris and abnormal pigmentation of the iris. Pathologic changes in the retina nad choroid were noted in many instances. Abortive attempts were made to trace the distribution of the aluminium through the tissues by staining reagents. On the clinical and experimental evidence, it is concluded that the eye is by no means inert to aluminium.

In an appendix, protocols of the experimental study are summarized, and the report on the histologic specimens is fully illustrated. The article contains nineteen illustrations, including several colored plates.

W. ZENTMAYER.

INDIRECT GUNSHOT INJURY OF THE EYE SIMULATING ELLIOT'S TREPHINING OPERATION. A. LOTIN, Vestnik oftal. **26: 70, 1947.**

A private aged 20 gave a history of having been injured in the left eye three years previously. A smooth linear scar, 3 cm. long, was visible at the left upper lid, at the inner orbital wall near the brow. It was not adherent to the orbital bone. The left eye presented a classic, oval trephine opening, at the limbus at 12 o'clock, with a filtering scar and a complete small coloboma of the iris. The fundus was normal, and vision was corrected to 0.9. At the hospital where he was treated after the injury no operative intervention was recorded. Evidently, the bullet caused the perforation of the sclera and injury of the iris, simulating a perfect Elliot trephination with iridectomy.

O. SITCHEVSKA.

Methods of Examination

APPEARANCE OF THE NORMAL FUNDUS AS STUDIED BY STEREO-OPHTHALMOSCOPY. ARCHIMEDE BUSACCA, Arch. d'opht. **7: 361, 1947.**

By means of the Goldmann slip lamp and with a contact glass modified by the author, stereoscopic examination of the fundus of the eye is possible; for this reason, the author uses the term stereo-ophthalmoscopy. He describes four different planes of the retina which can be identified by this method of examination. The first is the plane corresponding to the internal limiting membrane of the retina. The plane between the retina and the choroid has three aspects: the retinal pigmentary, the anterior choroidal and the specular plane. These three planes are difficult to separate. The third plane is the plane of the large choroidal vessels, and the fourth is that of the sclera. These planes, of course, are identified with the use of a narrow slit. The author believes that by this method a much more careful study of the fovea centralis and the macular region is possible. The method allows better correlation of the facts known concerning the vessels, their confirmation and structure, and the

relation of the planes and layers described in the different portions of the eye. With the use of his modification of the contact lens, he finds it possible to examine any part of the fundus. The subject is presented in some detail.

S. B. Marlow.

Qualitative and Quantitative Perimetry with Monochromatic Targets and with White Targets of the Same Luminous Intensity. P. Matteucci, Rassegna ital. d'ottal. **13:** 36, 1946.

The author studied fields of vision using monochromatic targets of equal subjective brilliance, as determined for each subject by means of flicker photometry. Perimetric examination was performed after adaptation to darkness, or after adaptation to a gray surface having an illumination equal to the gray surface of the perimeter. Behavior of the limits of the field for color was variable, and the limits were different even when monochromatic targets of the same size and brilliance were used. In quantitative perimetry the eye shows greater sensitivity to differences in contrast than to variation in size of test objects used. The results the author obtained differ greatly from those obtained by previous investigators, who used, under similar experimental conditions, spectral targets more or less monochromatic having equal energy content or luminosities. From these variations in the retinal sensitivity for the same color and the existence of factors not easily controllable, it is hard to define the limits of the visual field for colors, even if an average spectral visibility curve for peripheral vision is adopted. He expresses doubt as to the accuracy and value of employing colors in clinical perimetry.

G. B. Bietti—J. J. LoPresti.

Neurology

Ocular Symptoms of Poliomyelitis. Annotation, Brit. M. J. **2:** 620 (Oct. 18) 1947.

Kindt and Knudtzon (*Acta ophth.* **24:** 295, 1946) report on an epidemic of poliomyelitis in which 279 patients were affected: Thirty-seven patients showed bulbopontile lesions, 23 of whom had ocular symptoms; of these, 5 were under the age of 15 and 3 of them died; of the 18 adults, 2 died. Diplopia was the first symptom in 3 patients. In the other patients the ocular symptoms came on between four and eleven days after the onset. In 20 of the 23 patients the diplopia was combined with blurred vision. The diplopia was constant in some and transient in others. Nystagmus was present in 6 patients and unilateral ptosis in 1 patient. Paresis of the third nerve was observed in 3 patients. Paresis of the ocular muscles was regarded as nuclear in origin, and paralysis of the associated ocular movements, observed in 5 patients, as supranuclear in type.

The authors conclude that the frequency of ocular symptoms varies in different epidemics. Paresis of the sixth nerve, usually unilateral and transient, is the most frequent; paresis of the third nerve, rarely total and in most cases occurring with ptosis, with or without some degree of ophthalmoplegia, is next. Paresis of accommodation was noted in other epidemics. Trochlear paresis was recorded only once in the literature. Nystagmus, in conjunction with paresis of the ocular muscles, was

extremely frequent. Optic neuritis leading to atrophy of the optic nerve may be present. These ocular symptoms, though benign, are important as expressions of a highly localized and dangerous form of poliomyelitis.

ARNOLD KNAPP.

PATHOGENESIS AND PATHOPHYSIOLOGY OF COAL MINER'S NYSTAGMUS. M. PECHDO and L.-L. GAYRAL, Arch. d'opht. **7:** 521, 1947.

The authors review the work which has been done on this condition and discuss the various hypotheses which have been proposed to explain it. They express the belief that pendular nystagmus in coal miners is due to an intoxication of the nerve centers by methane (firedamp) and that the site of the lesion is in the neighborhood of the nuclei and pathways of the mesencephalon concerned with nystagmus. More particularly, they believe that this nystagmus may well correspond to the system which controls reflex fixation and fusion. Nystagmus is a symptomatic expression of lesions of these pathways or centers. Finally, they assert that there is no reason to preserve the mechanical theory of fatigue or of amblyopia arising from insufficient light. They have no explanation as to why nystagmus develops in some miners and not in others. They refer to the compensation aspect of the problem as it exists in Belgium and France, as compared with other countries.

S. B. MARLOW.

Operations

THE USE OF THE MASSETER, TEMPORALIS AND FRONTALIS MUSCLES IN THE CORRECTION OF FACIAL PARALYSIS. W. MILTON ADAMS, Plastic & Reconstruct. Surg. **1:** 216, 1946.

Of the methods used to correct the defects of facial paralysis, the best is nerve grafting. Unfortunately, this can be done in only a limited number of cases. The next best method is muscle substitution. This permits some motion without the associated distortion that nerve substitution produces. Fascial strips give a better primary result, but no motion is obtained and sagging is apt to recur.

For the closure of the eyelids, a strip of the temporalis muscle is transplanted into the margin of the upper and lower lids. While not perfect, this procedure is worth while. Motion to a paralyzed brow is obtained by transplanting a band from the active fellow frontalis muscle.

L. P. GUY.

RECENT ADVANCES IN OPHTHALMIC SURGERY. ALSTON CALLAHAN, South. Surgeon **13:** 92 (Feb.) 1947.

The author discusses corneal transplantation, unilateral aphakia and scleral resection. Some of the newer technics and instruments used in corneal transplantation are shown by illustration. The technic of using a contact lens on the aphakic eye to overcome diplopia is described. A drawing of the operative technic of a scleral resection is shown, with a short review of the recent papers on this subject.

C. P. GRANT.

NYLON THREAD IN OCULAR SURGERY. P. HALBRON and H. AITOFF, Bull. Soc. d'opht. de Paris, November-December 1946, p. 30.

Halbron and Aitoff have found that nylon sutures are most resistant to traction, easily manipulated, have a smooth surface, cause no swelling

in tissue and produce no inflammatory reaction. Sterilization is easy by the usual methods, without loss of their properties. The authors have used the sutures clinically in fixation through the superior rectus muscle in cataract extraction, in the sewing of the flap in operations for glaucoma, in muscle surgery, in evisceration when a prosthesis is sewed into Tenon's capsule, for muscle retention suture in detachment operation and in all plastic operations about the eye. The nylon suture is readily removed.

L. L. MAYER.

Orbit, Eyeball and Accessory Sinuses

EXOPHTHALMOS WITH INTERMITTENT AGGRAVATION: A SPECIAL FORM OF VARIABLE EXOPHTHALMOS. RAFFAEL CAMPOS, Arch. d'opht. **7:** 390, 1947.

The author reports the case of a girl aged 16 who had been affected since childhood with exophthalmos of the left eye, which was increased passively by tilting the head forward and on crying and effort. A roentgenogram revealed round opacities, resembling phleboliths, in the upper outer portion of the orbit. Although the exophthalmos disappeared after one operation, it recurred at the end of a year. The second surgical approach, by means of the Krönlein technic, revealed saccular dilatations of the orbital veins. The exophthalmos was cured, and visual acuity, which had decreased to 2/10 before operation, rose to 5/10. In discussing the various forms of variable exophthalmos, the author suggests a new and more exact classification. He defines as exophthalmos with intermittent aggravation the type described here and insists that this form of exophthalmos may be produced not only by an angioma of the orbit but also by varicosity of the orbital veins.

S. B. MARLOW.

Pharmacology

VISUAL EFFECTS OF TRIDIONE. L. L. SLOAN and A. P. GILGER, Am. J. Ophth. **30:** 1387 (Nov.) 1947.

Sloan and Gilger found that after treatment with trimethadione ("tridione"; 3,5,5-trimethyloxazolidine-2-4 dione) acuity, brightness sensitivity, color discrimination and sensitivity to flicker showed temporary impairment when both the foveal field and a surrounding area of 6 to 10 degrees were illuminated to a high brightness. With continued exposure to the high brightness visual function improved, and tolerance to the visual side-effects developed with continued medication.

W. S. REESE.

Retina and Optic Nerve

CAPILLARY FRAGILITY AND CAPILLARY PERMEABILITY IN RELATION TO RETINAL HEMORRHAGES. R. L. SHANNO, J. Q. GRIFFITH JR. and W. O. LAMOTTE JR., Am. J. Ophth. **30:** 1556 (Dec.) 1947.

Shanno, Griffith and LaMotte conclude from their studies that rutin is probably of value in preventing further retinal hemorrhages in patients in whom the initial hemorrhage was associated with a generalized capillary fault.

W. S. REESE.

SOFTENING OF THE RETINA IN SECTORS AND DETACHMENT. PIERRE DOUCET, Arch. d'opht. **7**: 167, 1947.

Two cases are reported in which only the area supplied by an artery was affected. A triangular lesion resulted, at the apex of which there were arteritis and disturbance of the return circulation, and, farther out, thinning of the retina with lenticular plaques, appearing like peas on a veil. The base of the triangle was represented by fine, floating threads, the last vestiges of the membrane. At the equator occurred a retinal tissue, which differed in the 2 cases. In 1 case there was atrophy with pigmentation; in the other the retina appeared healthy. The author calls attention to the triangular shape of the lesion as a possible explanation for the production of detachment and tears as the result of disease of an artery.

S. B. MARLOW.

APPARENT BLINDNESS OF THE NEWBORN—GRAY PSEUDOATROPHY OF THE OPTIC NERVE. BEAUVIEUX, Arch. d'opht. **7**: 241, 1947.

The author first describes the case of an infant 4 months of age at the time of first examination, twenty-three years before, when he had given a poor prognosis because of the presence of dilated pupils and a grayish, atrophic appearance of both optic nerves. Nine months later the pupils reacted definitely to light, but the ophthalmoscopic appearance was unchanged. Still later, some vision was reported, as manifested by the child's attempt to grasp objects; and later still, visual acuity was reported to accord with the refractive error and nystagmus. Since the observation of this case, the author has seen 8 similar ones. He gives a brief review of the literature. He expresses the opinion that the condition should be known to all ophthalmologists in order that they may avoid the diagnostic error which he himself had made. Cases of this condition may be divided into two groups: (1) cases in which a satisfactory and rapid recovery of vision takes place, and a change in the ophthalmoscopic picture occurs, and (2) cases in which visual development is less satisfactory and a number of sequelae occur, such as chorioretinal pigmentation, posterior polar cataract, strabismus, nystagmus and high myopia. He discusses the atrophy from the point of view of syphilis, tuberculosis and alcoholism and of the action of a neurotropic virus. He points out that there are plausible arguments in favor of a delayed myelination of the optic pathways. He presents this evidence and discusses the role that is played by myelin in the transmission of the light stimulus. Two color plates illustrate the cases.

S. B. MARLOW.

SURGICAL CURE OF DETACHMENT OF THE RETINA WITH PERFORATION OF THE MACULA: REPORT OF A CASE. DOUCET, Arch. d'opht. **7**: 284, 1947.

In a case of high myopia, the author was able to reach the region of the tear by dividing the external rectus muscle. A successful result was obtained, with some improvement in vision. The author points out that there are two technical difficulties in the operation and expresses the belief that some procedure should be developed which will not completely destroy the macula and result in severe loss of vision.

S. B. MARLOW.

ANGIOMATOSIS OF THE RETINA IN AN INFANT. M. APPELMANS, Arch. d'opht. **7:** 489, 1947.

The author reviews the literature on this condition and presents a personal observation accompanied with extensive histologic study. As the result of his bibliographic research, he concludes that angiomatosis of the retina, improperly called von Hippel's disease, was known as far back as 1862. His personal case demonstrates that this disease may appear as early as the age of 2 years, as does glioma. The histologic study shows that the central external layers of the retina are irreversibly degenerative at an early age, at the time when the uveal tract and the globe itself are intact. The interpretation of the lesion is not easy, even at a relatively early stage. The initial change seems to consist in capillary proliferation. The lesions can undergo cystoid or cavernous degeneration. The proliferative activity of the retina is remarkable. Gliosis, melanosis, fibrous and reticuloendothelial reactions, detachment of the retina and degeneration of the optic nerve fibers seem to be secondary. Diagnosis of the ocular condition is imperative in the child. Enucleation of the globe is urgent in cases of glioma, whereas it may be deferred in cases of angiomatosis. Examination of the fundus of the eye furnishes exact indications of the extraocular lesions, especially in cases of angiomatosis of the nervous system. One may consider with certainty that some angiofibromas of the optic nerve belong to the capillary angiomatoses. If angiomatosis is of congenital origin, one should not be surprised to see these lesions occur in the first years of life, at the same time that gliomas of the retina occur. If there is pathologically active angioblast, the early age obscures the prognosis. The article includes a number of excellent photomicrographs, and a long bibliography is appended.

S. B. MARLOW.

Visual Tracts and Fields

PERIPHERAL AND CENTRAL DISTURBANCES OF THE VISUAL FIELDS: AN ASPECT OF DI-OPHTHALMOLOGY. N. A. STUTTERHEIM, Brit. J. Ophth. **31:** 721 (Dec.) 1947.

Stutterheim describes 2 cases of functional contraction of the visual field of each eye and diminished central vision (amblyopia), combined with various other symptoms of severe eyestrain, caused by asthenovergence. A third case of central amblyopia without peripheral contraction and with negative convergence is reported.

According to the author, these cases represent a form of disturbance of field or central vision, which, if one does not grasp the importance of kinetic factors, as revealed by the study of the bi-foves and its correlate, convergence, must lead to a somber prognosis. With kinetic treatment, however, the patient is effectively cured both of limitation of the peripheral fields and of failure of central vision.

W. ZENTMAYER.

Correspondence

MUSCLE SCHEMAS

To the Editor.—Dr. Adler's review of Dr. Epstein's book on "Strabismus" (ARCH. OPHTH. **39:** 840 [June] 1948), touches on a point that merits some discussion. Dr. Adler points out some errors, e. g., illustration 5 and statements on page 9 bearing on ocular torsion. Both these errors can be traced to the illustrations and legends no. 581 and 582 in Duke-Elder's "Text-Book of Ophthalmology" (London, Henry Kimpton, 1932, vol. 1, p. 595). Dr. Epstein simply took the illustrations and legends uncritically and used them in his book.

This uncritical repetition of wrong and misleading diagrams in book after book is unfortunate. A diagram on muscle action in Hansell and Reber's "Ocular Muscles," second edition (Philadelphia, P. Blakiston's Son & Co., 1912, p. 28) leads the authors to say that "in movement of the eyes up and to the right, the two muscles principally concerned are the right inferior oblique and the left superior rectus; down and to the left, the right inferior rectus and the left superior oblique, and so on . . ."

This misleading diagram and the incorrect statement, which must also have appeared in the earlier first edition, have been copied since in numerous textbooks. This diagram, with the confusing notation, is also found in Peter's "Extra-Ocular Muscles," third edition (Philadelphia, Lea & Febiger, 1941, p. 62, fig. 33), and even in so carefully written a book as Spaeth's "Principles and Practice of Ophthalmic Surgery," fourth edition (Philadelphia, Lea & Febiger, 1948, p. 210, fig. 155). It is also repeated, together with the incorrect statements, in Duke-Elder's "Text-Book of Ophthalmology," volume 1, pages 611 and 612. When Duke-Elder does not use this confusing muscle schema, he gives the action of the aforementioned muscles correctly, viz., in his "Practice of Refraction," third edition (Philadelphia, P. Blakiston's Son & Co., 1938, p. 198).

Some books do not use any muscle schema, possibly because of this tendency to confusion. However, this is not an unmixed blessing, as it makes the subject much more difficult for the student, and sometimes even catches the author off guard. Thus, in Berens and Zuckerman's "Diagnostic Examination of the Eye," (Philadelphia, J. B. Lippincott Company, 1946, p. 191), is the statement that "there is extorsion in looking upward and inward, or in looking downward and outward; and there is intorsion in looking upward and outward or downward and inward."

It was in an effort to eliminate the recurrent source of confusion from the aforementioned diagram that I searched for a simpler and safer muscle schema, one that would be all embracing and yet be easily remembered. This resulted in the development of the benzene ring muscle schema, with its fifteen diagnostic features.

JOSEPH I. PASCAL, M.D., New York.

37 West Ninety-Seventh Street (25).

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

The American Board of Ophthalmology.—The American Board of Ophthalmology wishes to make known that it does not evaluate, approve or disapprove any ophthalmic residency with respect to its filling the requirements for candidates for board examinations. Any candidate who qualifies for the board examination and completes the prerequisites as outlined in the syllabus will be accepted. A copy of the syllabus can be obtained from the secretary of the American Board of Ophthalmology, 56 Ivie Road, Cape Cottage, Maine.

UNIVERSITY NEWS

Annual Postgraduate Ophthalmologic Conference, Department of Postgraduate Medicine of the University of Michigan.—The department of ophthalmology of the University of Michigan Medical School will give its annual postgraduate conference from March 7 to 9, inclusive, 1949. The conference offers a review of fundamental principles through lectures, demonstrations and operative procedures by physicians of national prominence, as well as an opportunity to observe the application of modern developments in ophthalmology.

It is not designed to prepare practitioners for specialization; rather, its purpose is to give those who are now prepared to practice ophthalmology a new point of view and a new impetus for further study and investigation, as well as to offer to all in attendance the benefit of the experience of others in the subjects covered.

The fee for the course is $25, payable on application.

Ophthalmologists are to bring their ophthalmoscope, since one-half day will be devoted to clinical demonstration of numerous interesting conditions of the fundus related to general disease.

Rooms have been reserved at the Michigan Union, Ann Arbor, for physicians enrolled in this conference. If reservation is desired, request should be sent directly to the room clerk as soon as possible, as a limited number of beds have been allotted for this conference.

Detailed programs may be obtained from Howard H. Cummings, M.D., chairman, department of postgraduate medicine, University Hospital, Ann Arbor, Mich.

School of Orthoptics, Massachusetts Eye and Ear Infirmary.—A school of orthoptics has been started at the Massachusetts Eye and Ear Infirmary, in conjunction with Simmons College, in Boston. During the first three years students at the college take courses that will give them an adequate scientific background. Their fourth year is spent at the hospital, where practical and didactic work in orthoptics

and perimetry is given. This four year program leads to the degree of Bachelor of Science and the diploma in orthoptics. Miss Ann Stromberg is technical director of the practical aspects of the work at the hospital.

SOCIETY NEWS

The Ophthalmological Society of Australia (British Medical Association).—The eighth annual general and scientific meeting of the Ophthalmological Society of Australia (British Medical Association) was held at the University of Western Australia, Perth, commencing on Aug. 16, 1948 and continuing for the week. The scientific meeting was held in conjunction with the Section on Ophthalmology of the Australasian Medical Congress, Sixth Session, and the president of the section, Dr. J. Bruce Hamilton, occupied the chair. The principal guest was Prof. Frank B. Walsh, of the Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine.

The president of the Ophthalmological Society of Australia (British Medical Association), Claude Morlet, M.B., was precluded by illness from presiding at the annual general meeting of the society, and the chair was occupied in this case by the immediate past president. Members present included 5 from New South Wales, 5 from Victoria, 1 from Tasmania, 5 from South Australia and 8 from Western Australia.

Dr. Arthur H. Joyce was elected president of the society for the ensuing year, and Dr. E. J. McGuinness, vice president.

It is proposed to hold the ninth annual general meeting at Melbourne in the first week of October 1949, and the tenth annual general meeting at Brisbane in June 1950, in conjunction with the Australasian Medical Congress, Seventh Session.

Southern Section, Association for Research in Ophthalmology Organized.—On October 26, during the meeting of the Southern Medical Association in Miami, Fla., the Southern Section of the Association for Research in Ophthalmology was organized. Dr. Conrad Berens gave a brief résumé of the development and achievements of the national association. Dr. George Haik presented further work on beta irradiation for glaucoma. Dr. Alston Callahan was asked to serve as chairman of the Southern Section for the coming year. The following ophthalmologists attended: Drs. Conrad Berens, Shaler Richardson, George Haik, William Sayad, Don Boles, W. R. Johnson, William Hester, Karl Benkwith, Samuel McPherson, Carl Dunaway, Stacy Howell, Curtis Benton Jr., Hugh Parsons, E. R. Veirs, Frank Costenbader, Mason Baird, Philip Lewis and Alston Callahan.

Eastern Section of Association for Research in Ophthalmology.—The first meeting of the Eastern Section of the Association for Research in Ophthalmology was held Saturday afternoon, November 13, at Lenox Hill Hospital, New York. The 184 members and guests registered heard the following scientific program: "Ocular Changes Associated with Scrub Typhus," Dr. Harold G. Scheie and Dr. Wilfred E. Fry, Philadelphia; "Some Biologic Problems in Vision," Dr. Samuel Detwiler, New York; "Recent Concepts in Aqueous Humor

Dynamics," Dr. V. Everett Kinsey, Boston; "A Critical Discussion of Experimental Exophthalmos," Dr. George F. Smelser, New York.

The attendance at the meeting was a tribute to the quality of the program, as well as to the efforts of the sectional secretary, Dr. A. E. Braley, and his organizational committee.

Georgia Society of Ophthalmology and Otolaryngology.—The annual meeting of the Georgia Society of Ophthalmology and Otolaryngology will be held at the General Oglethorpe Hotel in Savannah on March 4 to 5, 1949.

The distinguished lecturers and their tentative subjects are: "Management of Glaucoma," Dr. Paul A. Chandler, Boston; "Management of Cataract," Dr. Jack S. Guyton, Baltimore; "Allergy of the Upper Respiratory Tract," Dr. Oscar C. E. Hansen-Pruss, Durham, N. C.; "Management of Otologic Problems in Children and an Otologic Survey," Dr. Marvin F. Jones, New York; "External Diseases of the Eye and Dacryocystitis," Dr. Ralph O. Rychener, Memphis, Tenn.; "Problems in Laryngology," Dr. Fletcher D. Woodward, Charlottesville, Va.

Association for Research in Ophthalmology.—The annual meeting of the Association for Research in Ophthalmology will be held at the Warwick Hotel in Philadelphia, June 6 and 7, 1949.

Authors desiring to present papers at this meeting should submit the titles of their papers to James H. Allen, M.D., University Hospitals, Iowa City.

Ophthalmological Society of Egypt.—The annual meeting of the Ophthalmological Society of Egypt will take place at the Memorial Ophthalmic Laboratory, Giza, Egypt, on Friday and Saturday, March 4 and 5, 1949, at 9 a. m. Medical practitioners, oculists or others are cordially invited.

PERSONAL NEWS

Dr. J. C. McCulloch Awarded Reeve Prize.—The University of Toronto Faculty of Medicine has announced that Dr. J. C. McCulloch has been awarded the Reeve Prize; this award is made for the best scientific research accomplished in any department in the faculty of medicine by one who has held an appointment on the staff for not more than five years.

Dr. McCulloch was awarded this prize for his investigations, in conjunction with Dr. R. J. P. McCulloch, entitled "A Hereditary and Clinical Study of Choroideremia"; this has added greatly to the knowledge of this previously obscure hereditary ocular condition. The disease was found in over 80 descendants of a family of 500 members who were studied.

Dr. J. C. McCulloch is ophthalmologist in chief at Toronto Western Hospital and was recently appointed associate in the department of ophthalmology, in the University of Toronto.

Book Reviews

Principles and Practice of Ophthalmic Surgery. By Edmund B. Spaeth, M.D. Fourth edition. Price, $15. Pp. 1,049, with 649 illustrations, containing 1,251 figures and 8 colored plates. Philadelphia: Lea & Febiger, 1948.

This standard textbook has been thoroughly revised to include all the recent advances in its field. The numerous additions to the text are largely in the form of liberal quotations from various sources. While the value of the volume as a reference work is greatly enhanced by them, the reviewer found it difficult at times to determine the author's own personal views. The chapter on pathology of the orbit has been greatly enlarged to include a full discussion on the medical, as well as the surgical, treatment of thyrotoxic and thyrotrophic exophthalmos. In decompression of the orbit in extreme cases of malignant exophthalmos, the author favors removal of its lateral wall rather than its roof. A rather full description of some of the more recent technics for integrated implants is given in the chapter on enucleation. The physiology of strabismus and its nonsurgical treatment are ably presented, and much new material has been added in the discussion on the surgical aspects of this subject. The author's great interest in plastic surgery is evidenced by the completeness with which this part of ophthalmic surgery is covered. The same is true of blepharoptosis, to which 65 pages are devoted. These chapters more truly represent the author's own personal views than do most of the others and constitute the most important part of the book. The subject of retinal separation is well discussed and in sufficient detail. The chapters on keratoplasty, radium therapy and goniotomy are only amplifications of opinions expressed by the contributing authors.

The great popularity of this book is amply deserved, and in each edition every effort has been made to eliminate the faults of its predecessor. This current volume represents the fourth rewriting, and it is well done. A few misspellings and typographic errors still exist to detract from an otherwise excellent work.

The book gives the ophthalmologist the current views on all surgical subjects in a clear and concise manner. The author is to be congratulated for again having brought forth a textbook of which he can be justly proud. It has had, and will continue to have, a prominent place in every opthalmologist's library.

JOHN H. DUNNINGTON.

Documenta Ophthalmologica. Volume II. Edited by F. P. Fischer Utrecht, Netherlands; A. J. Schaeffer, Los Angeles, and Arnold Sorsby, London. Amsterdam, Netherlands: Dr. W. Junk, 1948.

This second edition of the "Documenta Ophthalmologica" is a welcome addition to literature on recent advances in ophthalmology. It is prefaced by a fitting tribute to the memory of Selig Hecht by George Wald.

The table of contents is as follows: "In Memoriam: Selig Hecht," G. Wald, New York; "Physiologic Optical Studies," A. von Tschermak-Seysenegg, Prague; "Physiologic Optics of the Visualization of Roentgenograms," W. Bronkhorst, Bilthoven, and J. ten Doesschate and F. P. Fischer, Utrecht; "Measurements of Fusion Frequency in the Clinic," R. Weekers and F. Roussel, Liége; "Mechanical Properties of the Tissues of the Eye," J. ten Doesschate and F. P. Fischer, Utrecht; "Apparatus and Method for Clinical Recording of the Electroretinogram," Gosta Karpe, Stockholm; "Early Diagnosis of Siderosis Retinae by Use of Electroretinography," Gösta Karpe, Stockholm; "Introduction to Experimental Trachomatology," L. Poleff, Rabat.

The general makeup of this volume is similar to that of volume I, but, in the opinion of the reviewer, the subject matter is not so well chosen. It is hoped that the next volume will contain reviews on branches of ophthalmology in which there has been considerable advance in the last few years, yielding information of practical value.

FRANCIS HEED ADLER.

Optometry: Professional, Economical and Legal Aspects. By H. W. Hofstetter. Price, $6.50. Pp. 412, with 35 illustrations. St. Louis: C. V. Mosby Company, 1938.

"This book is intended as a reference and text for use in undergraduate courses in optometry to familiarize the student with various non-clinical aspects of the practice of optometry." The author states that he is "indebted to the American Optical Company for a grant which has enabled [him] to devote such time as was free from teaching duties toward completion of this edition." The book is of little use to medical men except to reveal the aims and methods of optometry. The author states the use of the title "doctor" by the optometrist rests on the feeling "that he earns the right to use it by inspiring confidence in the citizens of a community that he is qualified to do the things that an optometrist is expected to do. So long as the optometrist uses the title to keep himself classified as a member of the healing art in the same manner as a dentist uses his title, he has a reasonable claim to the use of the title."

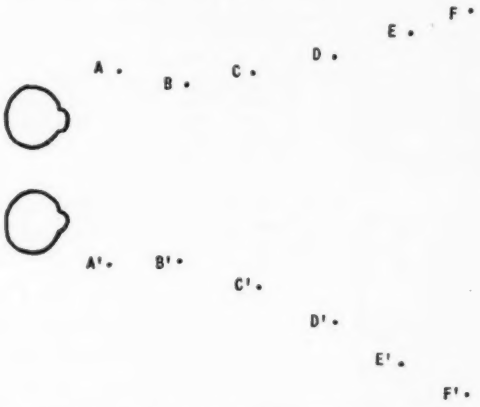
The author endeavors to strengthen the optometrist's claim to special ability in refraction and defines the "ophthalmologist as a physician certified by the American Board of Ophthalmology. The oculist is a physician without special certification who limits his practice to care of the eyes. The Eye, Ear, Nose and Throat Specialist is a physician without special certification who limits his practice to care of the eyes, ears, nose and throat."

These excerpts will suggest that organized optometry has neither changed its methods nor elevated its sights to the standard of a profession which it claims to be. It is hoped that its leaders will reshape its practice to permit a confident discharge of obligations to its patrons and justify a participation in the various public health and general welfare activities.

RALPH I. LLOYD.

Mathematical Analysis of Binocular Vision. By Rudolf K. Luneburg. Price, $2.50. Pp. 104. Published for the Dartmouth Eye Institute. Princeton, N. J.: Princeton University Press, 1947.

This work is, in the opinion of the reviewer, the most substantial advance in the mathematical theory of binocular vision which has been made in many years. Whether or not the concepts advanced will permit future improvement in the design of binocular microscopes, range find-



Set of pairs of vertical wires in Hillebrand's alley experiment.

ers, field glasses, slit lamps and other binocular instruments is, as Dr. Luneburg realizes, dependent on further experimental observations. These observations would be directed to the determination of what percentage of persons possess a visual space differing significantly from euclidean space.

It is the reviewer's thought that if the hypothesis is confirmed by further observation more immediate and feasible applications would be to orthoptic training, three dimensional motion pictures and television, particularly the last.

The basic thesis of the book is that visually perceived space is not Euclidean but is more readily described by the hyperbolic geometry of Lobachevski, although the applicability of Euclidean or Riemannian elliptic geometry in the instance of individual observers cannot be excluded.

In Euclidean space parallel lines are everywhere equidistant. Luneburg refers to Blumenfeld's repetition of Hillebrand's alley experiments as proof that visual space is not Euclidean. In alley experiments, the observer's head is fixed in a vertical position, and he is presented with two vertical wires, A and A', one placed to the right and the other to the left of the midline between the two eyes, as shown in the figure.

Additional pairs of vertical wires movable in a horizontal plane are provided, and the observer adjusts them so that the "walls" B, C, D, A, E, F and B', C', D', A', E', F' appear either everywhere equidistant

or everywhere parallel. The outcome of the experiment is that the walls are set neither equidistant nor parallel under either set of instructions to the observer but, rather, have the general shape shown in the figure. Furthermore, the instructions that the walls be made equidistant results (in general) in their placement outside the walls resulting from the instruction to make the walls parallel. As Luneburg says, this is "strong evidence" that visual space is hyperbolic, and not Euclidean.

Experiments at the Dartmouth Eye Institute with rooms, with variously curved walls and with variously curved windows, all of which, viewed binocularly, give the impression of the same rectangular room, can be adequately explained by the hypothesis that the "actual values" of elevation and horizontal deviation of the eyes "and especially the value of the convergence γ are insignificant for the visual sensation." As Luneburg correctly points out, "however, this theory leads us into difficulties when we try to understand the psychological fact of judging size independent of localization." An object first viewed at a distance of 1 meter and then at a distance of 10 meters appears to be of substantially the same size, although the area of its retinal image has varied by a factor of 100 to 1. This phenomenon, known as "size constancy," indicates that the human visual system can allow for, and hence must "perceive," distance. The existence of size constancy leads Luneburg to "the introduction of the convergence γ as a significant element of binocular vision." On first consideration, it may seem improbable that the "actual value" of convergence should be able to play a part in binocular vision, while the "actual value" of elevation or horizontal deviation of the eyes does not. It has been indicated (Irvine, S. R., and Ludvigh, E. J.: Is Ocular Proprioceptive Sense Concerned in Vision? ARCH. OPHTH. **15:** 1037-1049 [June] 1936), however, that the ocular muscles lack proprioceptive sense and that human vision relies on "innervation sense." It is thus possible that the degree of convergence or the distance of an object may be "perceived," although the amount of contraction or relaxation of the internal and external rectus muscles is not.

Luneburg proceeds to the analytic derivation of the expressions for the walls of distorted rooms equivalent to rectangular rooms. He then asks which of the geometries of constant curvature, elliptic, Euclidean or hyperbolic, is best able to account for the phenomenon of size constancy. Luneburg finds that over the critical region of distances from 1 to 25 meters only the hyperbolic geometry can account for the relative constancy of the ratio between apparent and physical size. Luneburg then derives theoretic frontal plane horopters, assuming that hyperbolic geometry is the proper geometry for binocular visual sensations. These horopters resemble the Hering-Hillebrand deviations from the Vieth-Müller circles over the region $\pm$ 25 degrees from the midline between the eyes. However, at more eccentric positions the horopters deviate from the classic horopters. Further experimentation is, as Luneburg points out, necessary.

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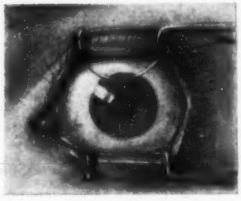

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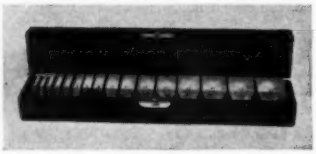

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